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Contrast-induced Nephropathy: Comparative Effectiveness of Measures to Prevent Contrast-induced Nephropathy

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions as well as new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether or not assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) for draft research questions and reports or to join an e-mail list to learn about new programs, products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the endusers of research and sought their input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. As a result, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

Here is the list of Key Informants who participated in developing this report:

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts with broad expertise and perspectives; divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Contrast-induced Nephropathy: Comparative Effectiveness of Measures to Prevent Contrast-induced Nephropathy

Structured Abstract

Objective: To evaluate the comparative effectiveness of different interventions (including intravenous (IV) fluids, N-acetylcysteine, sodium bicarbonate, and statins, among others) to reduce the risk of developing contrast-induced nephropathy (CIN) after receiving low osmolar contrast media (LOCM) or iso-osmolar contrast media (IOCM).

Data Sources: We searched for original published studies in MEDLINE®, Embase and the Cochrane Library through October 28, 2013. We also searched clinical trials.gov and the Scopus database for other studies.

Methods: Two reviewers independently reviewed each article for eligibility. For each study, one reviewer extracted the data and a second reviewer verified the accuracy. Both reviewers assessed the quality of each study. Together, the reviewers graded the strength of the evidence on preventing CIN and other adverse outcomes for the comparisons of interest. After the data were abstracted, the team quantitatively pooled the results of studies that were sufficiently similar, using the DerSimonian and Laird random effects model. We considered a 25 percent relative risk difference to be clinically important.

Results: We found a total of 136 studies of interventions to prevent CIN, including 63 randomized controlled trials (RCTs) comparing N-acetylcysteine with IV saline versus IV saline with or without a placebo, 23 RCTs comparing IV sodium bicarbonate versus IV saline, four RCTs comparing IV sodium bicarbonate versus N-acetylcysteine plus IV saline, four RCTs comparing a statin versus a placebo (only including studies in which contrast media was administered intra-arterially (IA)), five RCTs comparing an adenosine antagonist versus IV saline, and six RCTs investigating hemodialysis or hemofiltration versus IV saline. Although we found many studies investigating other interventions, the evidence generally was insufficient to support conclusions regarding the comparative effectiveness of those additional interventions. The studies were published between 1998 and 2013.

The strength of evidence was low that high-dose N-acetylcysteine (> 1200 mg/day) was more effective than IV saline in preventing CIN (pooled risk ratio (RR): 0.70; 95% confidence interval (CI): 0.50 to 1.0), consistent with a clinically important benefit, and a number needed to treat of 21 (CI: 13 to 172). The strength of evidence was low that low-dose N-acetylcysteine (1200 mg/day or less) had a small clinically unimportant effect on the risk of CIN compared with IV saline (RR: 0.80; 95% CI): 0.60 to 0.90). The benefit of N-acetylcysteine was most apparent when IA LOCM was used. The strength of evidence was low that IV sodium bicarbonate did not differ from IV saline in the risk of CIN (RR: 0.80; CI: 0.5 to 1.2. The strength of evidence was moderate that using a statin plus IV saline was more effective than IV saline alone in preventing CIN (RR: 0.5; CI: 0.4 to 0.8). The effect of statins is consistent with a clinically important benefit, and has a number needed to treat of 45 (CI: 30 to 217). The strength of evidence was low that use of hemodialysis versus IV saline to prevent CIN did not reduce the risk of CIN and may

even be harmful (RR: 1.4; CI: 0.9 to 2.2). All other comparisons had insufficient evidence to determine relative effectiveness in preventing CIN.

Conclusions: Of all the interventions that have been used in studies to reduce the risk of CIN, the only ones with evidence of a clinically important benefit over use of IV fluids alone are high-dose N-acetylcysteine with IV saline (low strength of evidence) and statins with IV fluids (moderate strength of evidence).

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Executive Summary

Background

Kidney failure is one of the most serious adverse effects that can occur after intra-vascular administration of contrast media in diagnostic or therapeutic procedures. The reported incidence of contrast-induced nephropathy (CIN) varies, but it is a leading cause of hospital-acquired kidney failure.[1] CIN is usually defined as an impairment of renal function with an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology. Though renal function returns to normal in the majority of patients, it can progress to acute kidney injury and chronic kidney failure in a small proportion of patients who develop CIN. Due to increasing use of contrast media in radiologic and cardiologic procedures, and the increasing prevalence of populations vulnerable to CIN (i.e., people having chronic kidney disease, diabetes mellitus, or hypertension, as well as the elderly), kidney failure due to CIN is a substantial concern. Numerous strategies have been used to try to prevent CIN. These strategies include: oral hydration; volume expansion with sodium chloride or bicarbonate or a combination of both; administration of N-acetylcysteine; withdrawal of metformin, ACE (angiotensin-converting-enzyme) inhibitors, angiotensin II receptor blockers, or non-steroidal anti-inflammatory drugs; hemofiltration or hemodialysis; statins; use of low osmolar or iso-osmolar, non-ionic, contrast media; and reducing the volume of contrast media administered. Despite these varied strategies, there is still no clear consensus in clinical practice about the most effective intervention to prevent or reduce CIN. We therefore sought to perform a comprehensive systematic review of the effectiveness of different measures for preventing CIN.

As most of the studies investigating CIN were conducted in patients who underwent intra-arterial procedures, the need for prevention strategies for patients undergoing intravenous procedures is controversial. To better understand the results, we sought to separately analyze patients who underwent intravenous versus intra-arterial contrast media, as these groups may have distinctly different risk profiles and susceptibility of developing CIN. We also sought to perform a separate analysis for patients receiving iso-osmolar contrast media (IOCM) or low osmolar contrast media (LOCM), the two types of contrast media in regular clinical use today. There are conflicting results from studies that have compared CIN risk of IOCM versus LOCM. ICOM is more expensive than LOCM. It is unclear whether the additional cost of IOCM is accompanied by a reduced risk of CIN. Also, it is not entirely clear how image quality and the risk of CIN differ between LOCM and IOCM.[2, 3]

Key Question

Key Question: In patients undergoing imaging studies requiring intravenous or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy (CIN), for the outcomes of incidence of CIN, chronic kidney disease (CKD), end stage renal disease (ESRD), mortality, and other adverse events?

Data Sources

We searched the following databases for primary studies published through October 28, 2013: MEDLINE®, EMBASE®, and the Cochrane Library. In addition, we looked for conference proceedings and other reports by searching the Scopus database. We reviewed the reference lists of relevant articles and related systematic reviews to identify original journal articles and other reports the database searches might have missed. We also searched ClinicalTrials.gov to identify on-going studies. We did not search for data held by the U.S. Food and Drug Administration (FDA.)

Study Eligibility Criteria, Participants, and Interventions

We followed the population, interventions, comparators, outcomes, timing, and setting (PICOTS) framework in developing the criteria for including studies in the review, and included studies of patients of all ages with low, moderate, or high risk of developing CIN. We included randomized controlled trials (RCTs) of any intervention to prevent CIN (including administration of N-acetylcysteine, sodium bicarbonate solution, sodium chloride solution, statins, adenosine antagonists, diuretics, vasoactive drugs, antioxidants, dopamine, and renal replacement therapy), in which the study groups received either IOCM or LOCM via intravenous or intra-arterial injection. Studies had to report on at least one of the outcomes listed in the Key Question. In our protocol, we planned to consider observational studies comparing strategies for preventing CIN if no RCTs addressed a comparison of interest, but we did not include observational studies in the final report because RCTs were available on the identified comparisons of interest.

Study Appraisal and Synthesis Methods

The titles and abstracts were independently screened by two reviewers. Inclusion at the title screening level was liberal; if a single reviewer believed an article might contain relevant information, the article was moved to the abstract level for further screening. When reviewing abstracts followed by the full text of articles, both reviewers had to agree on inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third expert member of the team. At random intervals during screening, quality checks by senior team members were performed to ensure that eligibility criteria were applied consistently.

We performed de novo meta-analyses of all studies on a given comparison if the studies were not too heterogeneous by qualitative or statistical criteria. Pooled risks were calculated using a random effects model using the method of DerSimonian and Laird.[4 16047] Statistical heterogeneity was assessed using the I-squared statistic.

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:[5]

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?

- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

Answers of "Yes" were given a score of one, and answers of "No" or "Unclear" were given a score of zero. To simplify the presentation of the assessments of study quality, we combined the ratings of the five items into an overall rating of potential risk of bias as low, medium, or high. We used the assessment of the first three items (covering selection bias and performance/detection bias) as the starting point, with a cumulative score of three designated as low risk of bias, two or one as medium risk of bias, and zero as high risk of bias. The overall rating of risk of bias was downgraded if there was also a concern about either incomplete reporting or selective outcome reporting. When assessing the risk of bias, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing.

The team graded the strength of evidence (strength of evidence) on comparisons of interest for the key outcomes, focusing mainly on the incidence of CIN, for which the most evidence was available. We used the grading scheme recommended in the Methods Guide[6] and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.[6]

Following the guidance of the GRADE Working Group [7], we rated evidence as precise if the total number of patients exceeded an optimum information size, and the 95% CI excluded a risk ratio of 1.0. We rated the evidence as imprecise if the 95% CI did not exclude the possibility of a clinically important benefit or harm (i.e., RR less than 0.75 or greater than 1.25) despite having an optimum information size. For the main outcome of interest, CIN, we used an optimum information size of 2000 based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative risk difference of 25%). For less frequent adverse outcomes, we used an optimum information size of 10,000 based on an expected 0.02 probability in the comparison group and a minimally important relative risk difference of 25%. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. We classified the strength of evidence pertaining to each comparison into four category grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the strength of evidence could be upgraded.

Organization of This Report

The following results section reports on a number of comparisons. We report in detail on comparisons for which substantial evidence exists. The comparisons are ordered according to the most commonly used preventive interventions (N-acetylcysteine plus intravenous saline versus intravenous saline, intravenous sodium bicarbonate versus intravenous saline, N-acetylcysteine plus intravenous saline versus intravenous sodium bicarbonate, statins plus intravenous saline versus intravenous saline, adenosine antagonists plus intravenous saline versus intravenous saline, and renal replacement therapy versus intravenous hydration). At the end of the results section, we refer to information about other "miscellaneous comparisons." Details on those comparisons appear in an appendix.

Results

The literature search revealed a total of 136 studies on interventions for preventing CIN, including 63 RCTs on N-acetylcysteine, 23 RCTs on intravenous sodium bicarbonate, eight RCTs on statins, five RCTs on adenosine antagonists, and six RCTs on use of hemodialysis or hemofiltration to prevent CIN. We included in the meta-analyses 44 RCTs investigating N-acetylcysteine with intravenous saline versus intravenous saline with or without a placebo (37 studies using only intra-arterial contrast media, 6 studies using intravenous contrast media, and 1 study using both), 13 RCTs investigating the use of sodium bicarbonate versus intravenous saline (11 studies using only intra-arterial contrast media, one study using only intravenous contrast media, and one study using either intra-arterial or intravenous contrast media), four RCTs investigating use of intravenous sodium bicarbonate versus N-acetylcysteine plus intravenous saline (3 studies using intra-arterial contrast media, and one study using intravenous contrast media), four RCTs investigating use of a statin versus a placebo (all studies using intra-arterial contrast media), four RCTs investigating use of an adenosine antagonist with intravenous saline versus intravenous saline alone (3studies using intra-arterial contrast media, and 1 study using intravenous contrast media), and three RCTs investigating use of hemodialysis versus intravenous saline alone (all studies using intra-arterial contrast media, one of which also included some patients receiving intravenous contrast media). The results of these studies were published between 1998 and 2013.

Using a random effects model to pool studies comparing N-acetylcysteine with intravenous saline versus intravenous saline with or without a placebo, the overall pooled risk ratio (RR) for CIN was: 0.70 (95% confidence interval (CI): 0.50 to 1.0) for high-dose N-acetylcysteine (> 1200 mg/day), indicating a small clinically important benefit with a number needed to treat of 21 (CI: 13 to 172), and low strength of evidence; and 0.80 (95% CI: 0.60 to 0.90) for low-dose N-acetylcysteine (1200 mg/day or less), indicating a small clinically unimportant effect . In sensitivity analyses, the pooled RR for CIN was: 0.70 (CI: 0.5 to 1.0) for high-dose N-acetylcysteine when intra-arterial contrast media was used; 0.30 (CI: 0.1 to 1.1) for high-dose N-acetylcysteine when intravenous contrast media was used; 0.80 (CI: 0.6 to 0.9) for low-dose N-acetylcysteine when intra-arterial contrast media was used; 0.70 (CI: 0.3 to 1.4) for low-dose N-acetylcysteine when intravenous contrast media was used; 0.70 (CI: 0.6 to 0.8) for N-acetylcysteine when LOCM was used; and 1.20 (CI: 0.9 to 1.8) for N-acetylcysteine when IOCM was used based on a small set of five studies on patients with varying comorbidities. The CI was wide enough for N-acetylcysteine when IOCM was used to suggest possible harm without any indication of a clinically important benefit. When we examined how the RR estimates varied according to baseline characteristics of the study population, we did not observe any meaningful difference by age, baseline renal function, or the presence or absence of diabetes mellitus. The strength of evidence was low that N-acetylcysteine with intravenous saline did not differ from intravenous saline with or without a placebo in the need for renal replacement therapy, cardiac events, or length of hospitalization. Studies addressing these outcomes had medium study limitations, and were consistent, but imprecise. We found insufficient evidence to draw conclusions about the effect of N-acetylcysteine on mortality.

In studies comparing intravenous sodium bicarbonate with intravenous saline, the overall pooled RR of CIN was 0.80 (95% CI: 0.5 to 1.2). The point estimate of the RR indicated a clinically unimportant difference in the risk of CIN. The associated CI ruled out a clinically

important increase in CIN, but did not rule the possibility of a clinically important decrease in CIN. The strength of evidence was low for this conclusion because the studies had medium study limitations with inconsistent results. The strength of evidence also was low that intravenous sodium bicarbonate did not differ from intravenous saline in mortality or the need for renal replacement therapy. Studies addressing these outcomes had medium study limitations, and were consistent, but imprecise. We found insufficient evidence to draw conclusions about how intravenous sodium bicarbonate compared to intravenous saline in the risk of cardiac events and length of hospitalization.

In the RCTs comparing intravenous sodium bicarbonate with the combination of N-acetylcysteine and intravenous normal saline, the pooled RR for CIN was 0.93, indicating no clinically important difference. However, the studies were inconsistent and the 95% confidence interval was so wide (0.40 to 2.1) that we cannot rule out the possibility of either an important decrease or important increase in risk. Therefore, the strength of evidence was insufficient to support a conclusion about the comparative effectiveness of these two interventions. The evidence also was insufficient to draw conclusions about potential differences between the two interventions in mortality, cardiac events need for renal replacement therapy, or length of hospitalization.

The strength of evidence was moderate from studies that compared use of a statin plus intravenous fluids versus intravenous fluids alone, showing a clinically important and statistically significant reduction in CIN (pooled RR 0.5; 95% CI: 0.4 to 0.8) with a number needed to treat of 45 (95% CI: 30 to 217. Four studies with a total population of 3647 were included to reach this conclusion. These studies had a low to medium risk of bias, were designed to measure CIN as the primary outcome, and consistently showed a benefit in reducing CIN in favor of the statin drug with relatively precise estimates. The number needed to treat was higher for statins than for high-dose N-acetylcysteine despite having a lower RR estimate because of differences between the two groups of studies in the baseline risk of CIN. The strength of evidence was low that mortality and the need for renal replacement therapy did not differ between statins plus intravenous fluids versus intravenous fluids alone. . Studies addressing these outcomes had medium study limitations, and were consistent, but imprecise. We found insufficient evidence to draw conclusions about the effect of statins on cardiac events or length of hospital stay when given to prevent CIN.

The strength of evidence was insufficient when studies compared adenosine antagonists plus intravenous saline with intravenous saline alone because the confidence interval was so wide that we could not rule out either a clinically important decrease or a clinically important increase in CIN (pooled RR 0.8, 95% CI: 0.1 to 8.2). The strength of evidence was insufficient to make conclusions about the impact of adenosine antagonists on the need for RRT, cardiac events, mortality, or length of hospitalization.

The pooled analysis for the three studies of hemodialysis compared with intravenous saline yielded a pooled RR of 1.4, which is consistent with a clinically important increased risk of CIN. The corresponding 95% CI was 0.9 to 2.2, which is consistent with an increased risk or no important difference. Although the studies on hemodialysis had high risk of bias, the results were consistent enough and precise enough to provide low strength of evidence that hemodialysis does not reduce the risk of CIN when compared to intravenous saline. Two RCTs compared hemofiltration to intravenous saline and reported that patients with severe CKD may have a lower incidence of CIN with hemofiltration, but the strength of evidence was insufficient to support a conclusion. The strength of evidence was insufficient to make conclusions about the

impact of using hemodialysis or hemofiltration on mortality, cardiac events, the need for subsequent renal replacement therapy, or the length of hospitalization.

Although we found many studies investigating other interventions (see Table A), the evidence generally was insufficient to support conclusions regarding the comparative effectiveness of those additional interventions.

Table A. List of miscellaneous comparisons

Intervention	Comparisons
N-acetylcysteine	Dialysis, ascorbic acid, nebivolol, atorvastatin, aminophylline, theophylline, fenoldopam, misoprostol
Intravenous sodium bicarbonate	Acetazolamide, long-term versus short-term intravenous sodium bicarbonate, intravenous saline in five percent dextrose, oral sodium bicarbonate
N-acetylcysteine plus intravenous sodium bicarbonate	Intravenous saline and N-acetylcysteine, furosemide plus saline plus N-acetylcysteine, placebo plus sodium bicarbonate, sodium bicarbonate
Diuretics (furosemide, mannitol, and acetazolamide)	Intravenous saline
Vasoactive agents (fenoldopam, calcium antagonists, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, beta-blockers	Intravenous saline
Antioxidants (probucol , pentoxifylline)	Different hydration regimens
Fluid administration (various)	Fluid administration (various)
Dopamine (or dopamine plus furosemide)	Dopamine, furosemide, mannitol, intravenous saline

Discussion

Of all the interventions that have been used in studies to reduce the risk of CIN, the only ones with evidence of a clinically important benefit over use of intravenous saline alone are high-dose N-acetylcysteine with intravenous saline (low strength of evidence with a number needed to treat ranging from 13 to 172) and statins with intravenous saline (moderate strength of evidence and number needed to treat ranging from 30 to 217). Intravenous sodium bicarbonate does not appear to be any more effective than intravenous saline (low strength of evidence) For other interventions and comparisons included in this report, the strength of evidence was insufficient to support a definite conclusion because, in general, the studies had important limitations, the comparators varied too much, the effects were inconsistent and imprecise, and the magnitude of effect was weak. Although usual care often involves administration of intravenous fluids, the evidence was insufficient to support a conclusion about the relative effectiveness of intravenous versus oral fluids, or whether fluids should be given before or after the procedure.

Our review shows that most strategies for preventing CIN present insufficient evidence of benefit. For clinicians who want to reduce the risk of CIN in patients receiving LOCM or IOCM, the best evidence of potential benefit was seen with use of N-acetylcysteine or a statin.

Despite the large body of evidence on N-acetylcysteine, the strength of evidence was low primarily due to limitations in the quality of many of the studies and inconsistency in results across studies, with the possibility of an effect too small to be clinically meaningful. The low strength of evidence helps to explain why N-acetylcysteine is not being used more often in clinical practice, and why professional organizations offer differing recommendations about the

use of N-acetylcysteine to prevent CIN. The joint American College of Cardiology/American Heart Association 2012 guideline recommends against use of N-acetylcysteine for patients receiving intra-arterial contrast in cardiac procedures, while the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury recommends using oral N-acetylcysteine with intravenous fluids in patients at increased risk for CIN. Our review provides modest support for the conclusion that high-dose N-acetylcysteine may offer a small clinically important benefit in some settings, although we did not see a significant difference in effectiveness according to the baseline risk of CIN. Of note, N-acetylcysteine is inexpensive, and appears to be safe.

The strength of evidence on statins was moderate, with a confidence interval suggesting at least a 20% relative reduction in the risk of CIN. Despite previous systematic reviews highlighting the existence of this evidence on the effectiveness of statins in lowering the risk of CIN, statins are not being used routinely in clinical practice to prevent CIN. Furthermore, we are not aware of any professional guidelines recommending their use for this indication. With increasing recognition of the beneficial cholesterol-independent vascular effects of statins, it may be time to reassess the role of statins in preventing CIN, especially since statins are readily available, easy to administer, and relatively inexpensive.

Our analysis concluded that intravenous sodium bicarbonate did not produce a clinically important decrease in CIN compared with intravenous saline, contrary to the conclusion of a recent meta-analysis[8] This difference in conclusions can be attributed to the fact that the other meta-analysis included five studies that used a combination of intravenous sodium bicarbonate and N-acetylcysteine, which we excluded from our analysis of the effects of sodium bicarbonate.

Future Research

Future studies of the comparative effectiveness of interventions for preventing CIN should stratify patients according to their baseline risk of CIN, especially since it may be difficult to detect a difference in patients having a low risk of CIN. Patients with normal or near normal serum creatinine may have a lower risk for developing CIN compared to those with higher serum creatinine levels. Also, patients with risk factors for CKD may have a higher risk of developing CIN than patients without such risk factors. Unfortunately, we had a limited ability to stratify the analysis according to baseline risk because almost all studies had a mixed patient population and did not report the results separately by baseline risk.

Since the evidence for a small benefit from high-dose N-acetylcysteine was not strong, more research is needed in this area also. Future research could examine whether the effectiveness of high-dose N-acetylcysteine differs by route of administration (oral versus intravenous), timing of administration (before versus after the procedure), or baseline risk of developing CIN. Given the evidence that intravenous sodium bicarbonate did not produce a clinically important reduction in CIN compared with intravenous saline, and did not differ in head-to-head comparisons with N-acetylcysteine, it may be difficult to justify additional RCTs of intravenous sodium bicarbonate unless new evidence emerges to suggest that particular regimens for administering sodium bicarbonate are more effective than the usual administration of intravenous saline, or that sodium bicarbonate has a benefit for particular groups of patients having a higher risk of developing CIN. The clinically important benefit of statins demonstrated in this analysis provides a rationale for further studies investigating whether the effect differs by statin dose, timing of administration, or baseline risk of the patient population.

Surprisingly little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving contrast media, despite the fact that current clinical practice often involves use of oral hydration alone for studies with intravenous contrast media. Oral hydration is a simple and potentially cost-effective strategy for preventing CIN, if shown to be as effective as intravenous saline. Unfortunately, very few studies investigated oral hydration versus intravenous saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus intravenous saline, especially for intra-arterial contrast procedures such as coronary angiography.

Finally, it is very difficult to apply the existing evidence to patients receiving intravenous contrast media because the vast majority of studies focused on patients receiving intra-arterial contrast media. The risk of CIN may be low enough with the intravenous administration of LOCM and IOCM to make it very difficult to demonstrate the effectiveness of an intervention for preventing CIN. To determine the effectiveness of interventions for preventing CIN in patients receiving intravenous contrast media, it may be necessary to perform large studies of patients having risk factors for developing CKD.

Conclusion

Of all the interventions that have been used in studies to reduce the risk of CIN, the only ones with evidence of a clinically important benefit over use of intravenous fluids alone are high-dose N-acetylcysteine with intravenous saline (low strength of evidence) and statins with intravenous fluids (moderate strength of evidence).

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Introduction

Background

Kidney failure is one of the most serious adverse effects that can occur after intra-vascular administration of contrast media in diagnostic or therapeutic procedures. The reported incidence of contrast- induced nephropathy (CIN) varies, but it is a leading cause of hospital-acquired kidney failure.[1] CIN is usually defined as an impairment of renal function, with an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology. Although renal function returns to normal in the majority of patients, it can progress to acute kidney injury and chronic kidney failure in a small proportion of patients who develop CIN. Clinicians are concerned about the risk of CIN because of increasing use of contrast media in radiologic and cardiologic procedures, and the high prevalence of populations vulnerable to CIN (i.e., people having chronic kidney disease, diabetes mellitus, or hypertension, as well as the elderly). Various types of imaging studies or procedures use intravenous or intra-arterial contrast media, including: intravenous pyelograms; brain, head and neck, body, or coronary computed tomograms (CT); cerebral, cardiac, or peripheral vascular angiograms; and radiologic therapeutic procedures. Contrast media is injected intravenous for CT and intra-arterial for angiograms and related interventional procedures. More than 62 million CT studies were performed in the United States in 2006 and the use of CT tripled between 1996 and 2010, from 52 studies per 1000 patients to 149 studies per 1000 patients.[2]

The reported incidence of CIN varies, but a reasonable overall estimate is that it occurs in about 2 percent of patients receiving intra-vascular contrast media.[1] Variation in the populations studied makes it difficult to determine whether the incidence of CIN has increased over time. Most of the estimates are derived from invasive angiographic studies, over the last few decades, using intra-arterial contrast media, which may have a higher risk of CIN than imaging studies using intravenous contrast media. One problem in determining the precise incidence of CIN is that many patients do not remain hospitalized for enough time after contrast administration to make the diagnosis. In addition, the use of serum creatinine as a marker of renal function has its limitations. It is often difficult to exclude other possible etiologies of elevations in serum creatinine. Furthermore, the incidence may vary according to the osmolality of contrast media used. Although there is consensus that the risk of CIN is highest with high-osmolar contrast media (HOCM), which has an osmolality five to eight times higher than plasma osmolality, HOCM is no longer used in clinical practice. It is unclear whether or not the risk of CIN differs between low-osmolar contrast media (LOCM), which has an osmolality two to three times plasma osmolality, and iso-osmolar contrast media (IOCM), which is isotonic to plasma. It is also often difficult to distinguish the effects of contrast media from the effects of physiologic confounders that could elevate the serum creatinine in patients undergoing radiologic studies. For example, blood flow to the kidneys could be compromised by emboli or vascular compression from catheter manipulation.[3, 4]

Numerous strategies to prevent CIN have been used, including: oral fluids; volume expansion with sodium chloride, sodium bicarbonate, or a combination of both; administration of N-acetylcysteine, statins, angiotensin converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers; withdrawal of nonsteroidal anti-inflammatory drugs; withdrawal of metformin; and hemofiltration or hemodialysis. Recent meta-analyses on the topic have yielded

contradictory results. A meta-analysis by Sun et al., 2013 concluded that the evidence on use of intravenous N-acetylcysteine to prevent CIN was too inconsistent to determine the efficacy.[5] Another meta-analysis, performed by Loomba et al., 2014,[6] concluded that N-acetylcysteine may help to prevent CIN in patients undergoing coronary angiography, but does not have any impact on clinical outcomes such as need for dialysis or mortality. A meta-analysis by Xie et al., 2014[7] concluded that statins given before angiography are effective in preventing CIN, but the optimum dose and duration for statin use are unknown. A recent review of randomized controlled trials (RCTs) of sodium bicarbonate administration for prevention of CIN revealed the conflicting nature of the evidence, with some studies showing benefit and others showing no benefit.[8]

In another meta-analysis, McDonald et al., 2013[4] concluded that the incidence of acute kidney injury was similar between patients receiving intravenous contrast media and patients receiving an imaging procedure without contrast media, raising the question of whether intravenous contrast media are even associated with an increased risk of CIN. With that question in mind, it is important to carefully examine the evidence on the effectiveness of interventions for preventing CIN while taking into consideration how the effectiveness may depend on the route of administration as well as the type of contrast media being used.

Despite the number of previous reviews, uncertainty persists about several issues, including:

1. The efficacy of oral fluids versus intravenous volume expansion in preventing CIN;[9, 10]
2. The optimal timing (pre- vs. post-contrast media administration or both), duration, and type of intravenous fluids used to prevent CIN[11];
3. The efficacy of low versus high dose N-acetylcysteine;
4. The efficacy of a combination of interventions, such as N-acetylcysteine plus sodium bicarbonate;
5. The efficacy of statins, taking into consideration dose and duration of the medication;
6. The efficacy of vasoactive drugs;
7. The efficacy of hemodialysis and hemofiltration relative to the invasive nature and cost of these interventions;
8. Whether any intervention is needed for intravenous contrast media procedures when there is uncertainty about whether intravenous contrast media is associated with CIN; and
9. Effect of the volume of contrast media administered, and the possibility of preventing CIN by keeping the volume of contrast media below a threshold.

Guidelines around contrast media administration have been published by a number of organizations. The 2007 American College of Radiology practice guideline focused on the correct administration of contrast media and the patients who are most likely to benefit from using LOCM instead of HOCM, rather than the evidence for or against different preventive measures. Guidelines on the prevention of CIN were published in 2007 by the Canadian Association of Radiologists,[13] and they were published following what they described as an "in-depth literature search with critical review"; however, no further details were included about the methods. Guidelines were also issued in 2006 by the CIN Consensus Working Panel, an international multidisciplinary group; these guidelines were based on an evidence review through 2005.[14] The method of synthesis varied among these guidelines and many were based on consensus opinions of clinical experts.

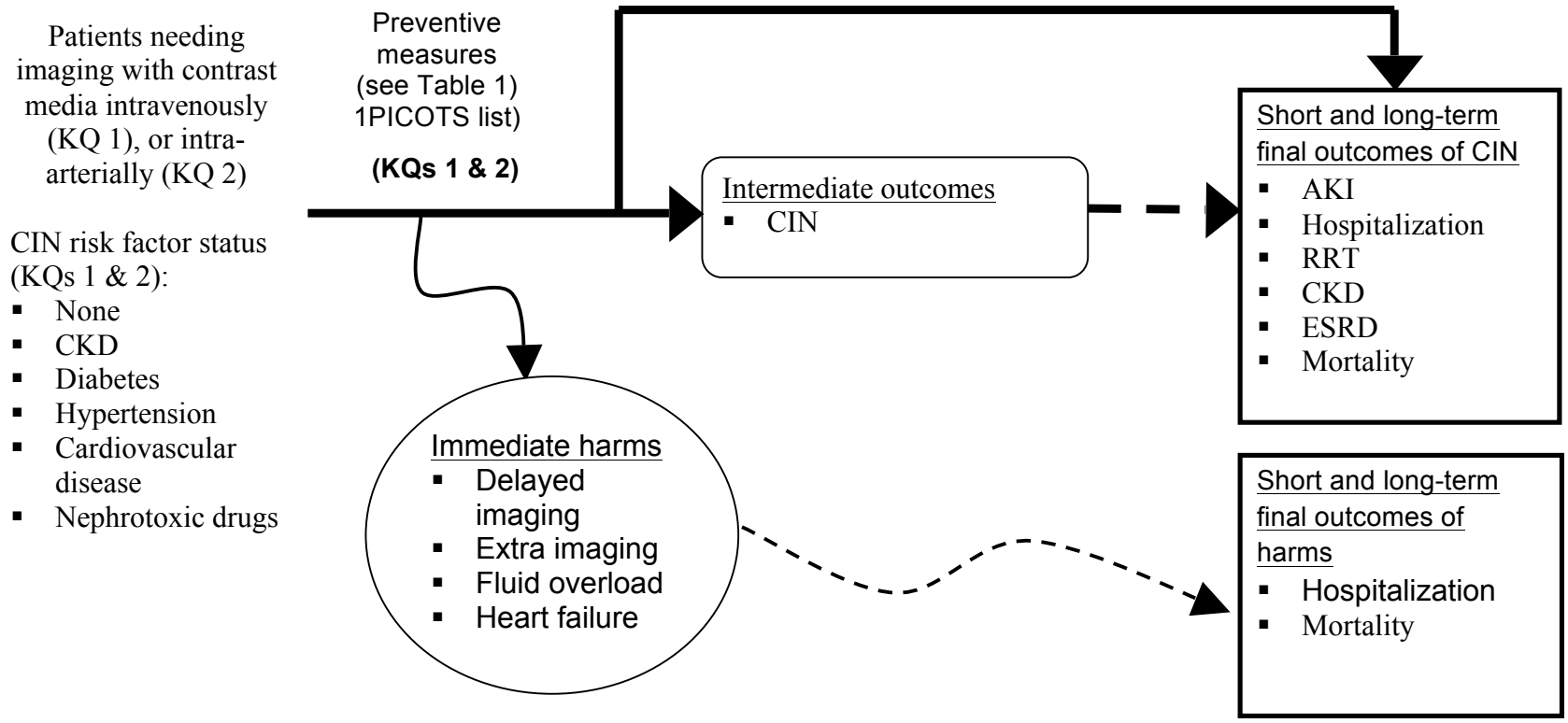
In light of the increasing use of contrast media in radiologic and cardiologic procedures, the

high prevalence of populations vulnerable to CIN (e.g., people having chronic kidney disease, diabetes mellitus, or hypertension as well as the elderly), and discrepant results from prior analyses, we sought to perform a comprehensive systematic review of this topic for the benefit of clinicians who wish to prevent CIN in patients undergoing imaging studies.

Scope of the Review

We reviewed studies that assess the effectiveness of one or more measures for preventing CIN in patients receiving either IOCM or LOCM, the two types of contrast media still in regular use (Figure 1 and Table 1). We included studies that reported on specific short-term or long-term outcomes (Table 2).

Figure 1. Analytic framework comparing the benefits and harms of different methods used to prevent contrast-induced nephropathy in patients receiving low osmolar or iso-osmolar contrast media.



AKI=acute kidney injury; CIN=contrast induces nephropathy; CKD=chronic kidney disease; ESRD=end stage renal disease; IOCM=iso-osmolar contrast media; KQ=Key question; LOCM=low-osmolar contrast media; RRT=renal replacement therapy

Table 1 PICOTS (populations, interventions, comparisons, outcomes, setting and timing) criteria for defining the scope of the review.

Populations	● All patients (including adults and children) undergoing procedures requiring LOCM or IOCM administration ● All patients regardless of their risk of developing CIN (as defined by clinical or demographic risk factors such as age, cardiovascular and other comorbidity, Cr level, etc.) ● Patients using contrast media for any type of imaging study
Interventions	● IV volume expansion with NaCl ● IV volume expansion with sodium bicarbonate ● IV volume expansion with NaCl and sodium bicarbonate ● IV or oral N-acetylcysteine, high-dose ● IV fluids without pharmacologic agents ● IV fluids with pharmacologic agents ● Oral fluids ● Oral statins (KQ2 only) ● IV dopamine ● IV fluids matched to urine output ● Discontinuation of metformin because of concern about inducing lactic acidosis ● Discontinuation of medications that could have adverse effects on kidney function (e.g., ACE inhibitors, angiotensin II receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs) ● Renal replacement therapy (RRT) (e.g., hemodialysis or hemofiltration)
Comparators (see Table 2)	● Usual care vs. any of the interventions listed above ● Volume expansion with NaCl vs. volume expansion with sodium bicarbonate ● Volume expansion with NaCl vs. volume expansion with NaCl and sodium bicarbonate ● Volume expansion with sodium bicarbonate vs. volume expansion with NaCl and sodium bicarbonate ● High-dose vs. low-dose N-acetylcysteine ● Timing and duration of above
Outcomes	● Short-term (≤7 days): a) Harms of prevention interventions o Imaging delay o Need for additional imaging o Fluid overload o Heart failure b) Renal function measures o Development of CIN as defined by change in Cr or change in GFR c) Renal disease-specific outcomes o Need for RRT (dialysis or hemofiltration) d) Other clinical outcomes o Mortality (in-hospital or within 7 days) o Cardiac outcomes e) Prolonged hospital stay ● Long-term (>7 days): a) Renal function measures o Development of CKD, including end stage renal disease (ESRD) o Rate of conversion to CKD at 3 and 6 months o Chronic change in kidney function b) Renal disease-specific outcomes o Need for RRT (dialysis, hemofiltration, or kidney transplant) c) Other clinical outcomes o Cardiac outcomes o Mortality in-hospital or at 3 or 6 months
Timing	● For short-term outcomes, any followup during hospitalization or within 7 days of procedure ● For long-term outcomes, followup for more than 7 days ● For observational studies, followup for at least 2 years.
Setting	● Inpatient and outpatient

Table 1 PICOTS (populations, interventions, comparisons, outcomes, setting and timing) criteria for defining the scope of the review (continued).

* Pharmacological agents of interest include: ACE inhibitors, ARBs, calcium antagonists, theophylline, aminophylline, dopamine, fenoldopam mesylate, atrial natriuretic peptide, statins, mannitol, MENSA fluid, allopurinol, furosemide, trimetazidine, anisodamine, probucol, and pentoxifylline.

ACE=angiotensin-converting enzyme; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; Cr=creatinine; ESRD=end-stage renal disease; GFR=glomerular filtration rate; IOCM=iso-osmolar contrast media; IV=intravenous; LOCM=low osmolar contrast media; NaCl=sodium chloride; RRT=renal replacement therapy

Table 2. Major interventions for preventing contrast-induced nephropathy, and main comparisons of interest (number of studies/total number of study participants).

	IV saline	IV bicarb	IV or oral NAC, high-dose	IV or oral NAC, low or high dose, plus IV bicarb	IV fluids with pharmacologic agents[†]	Adenosine antagonists	RRT-HD or HF	Statins	IV dopamine
IV saline	14/1932[‡]	13/2167	14/1932	7/1838	16/2212	5/477	6/1149	8/4719	3/213
IV bicarb					4/631				
IV or oral NAC, low-dose	31/5034								
IV or oral NAC, low or high dose	55/ 10,000	5/742			23/5126				

*These are the comparisons that had sufficient evidence to merit inclusion in this systematic review.
[†] Pharmacological agents include: ACE inhibitors, angiotensin receptor blockers, calcium antagonists, theophylline, aminophylline, dopamine, fenoldopam mesylate, atrial natriuretic peptide, statins, mannitol, MENSA fluid, allopurinol, furosemide, trimetazidine, anisodamine, probucol, pentoxifline, and benazepril.
[‡] Includes studies that compares all hydration regimens (oral and intravenous).

ACE=angiotensin-converting enzyme; ARB=angiotensin II receptor blockers; bicarb=bicarbonate; intravenous bicarb=intravenous volume expansion with sodium bicarbonate; intravenous saline plus bicarb=intravenous volume expansion with saline and sodium bicarbonat

Key Question

In patients undergoing imaging studies requiring intravenous or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy (CIN), for the outcomes of incidence of CIN, chronic kidney disease (CKD), end stage renal disease (ESRD), mortality, and other adverse events?

a. How does the comparative effectiveness of prevention measures vary by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate [GFR], or creatinine level)?
b. How does the comparative effectiveness of prevention measures vary according to the type of contrast media used (i.e., LOCM versus IOCM)?
c. How does the comparative effectiveness of prevention measures vary by characteristics of the interventions (e.g., dose, duration, and timing)?

Organization of This Report

The following results section reports on a number of comparisons. We report in detail on comparisons for which substantial evidence exists. The comparisons are ordered according to the most commonly used preventive interventions (N-acetylcysteine plus intravenous saline versus intravenous saline, intravenous sodium bicarbonate versus intravenous saline, N-acetylcysteine plus intravenous saline versus intravenous sodium bicarbonate, statins plus intravenous saline versus intravenous saline, adenosine antagonists plus intravenous saline versus intravenous saline, and renal replacement therapy versus intravenous hydration). At the end of the results section, we refer to information about other "miscellaneous comparisons." Details on those comparisons appear in an appendix.

Methods

Topic Refinement and Protocol Review

We developed the Key Question (KQ) with the input of a key informant panel that included experts in nephrology, radiology, cardiology, and primary care as well as representatives from the Food and Drug Administration and staff from the Agency for Health Care Research and Quality. We also recruited a technical expert panel to provide input on the protocol for the comparative effectiveness review.

Literature Search Strategy

We searched the following databases for primary studies through October 28, 2013: MEDLINE®, EMBASE®, and the Cochrane Library (see Appendix B for a detailed search strategy). We did not add any date limits to the search and developed a search strategy for MEDLINE, accessed via PubMed®, based on medical subject headings (MeSH®) terms and text words of key articles that we identified a priori. The search was not limited by language. In addition, we looked for conference proceedings and other reports by searching the Scopus database. We reviewed the reference lists of relevant articles and related systematic reviews to identify original journal articles and other reports the database searches might have missed. Scientific Information Packages were requested from a number of industry representatives/manufacturers, but no information was provided. We also searched ClinicalTrials.gov to identify on-going studies. We did not search for data held by the U.S. Food and Drug Administration (FDA). The FDA has not approved any interventions for the prevention of CIN.

We uploaded articles into DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based service for systematic review and data management. We used this database to track search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

Study Selection

We followed the PICOTS framework (Table 1) in developing the criteria for including studies in the review, and included studies of patients of all ages with low, moderate, or high risk of developing CIN. We anticipated heterogeneity in the pre-procedure risk assessment and reported on the heterogeneity as it was defined by the studies, which had to assess serum creatinine or GFR prior to and after contrast media injection. We only included studies in which the intervention group received either IOCM or LOCM via intravenous or intra-arterial injection. Studies had to report on at least one of the outcomes listed in the PICOTS framework. We included RCTs of comparisons detailed in the PICOTS, but focused the review on comparisons for which two or more studies reported on the same comparison. When we found interventions for which the comparisons were too heterogeneous to support an overall conclusion, we included a summary of the studies in the main report and placed details in the appendices.

In our protocol, we planned to consider observational studies if no RCTs addressed a comparison of interest. We did not include observational studies in the final report because RCTs were available on the comparisons of interest.

We evaluated previous systematic reviews on this topic to determine the extent to which they addressed our specific KQs.

Data Extraction

Due to the volume of literature, we first screened titles and then screened abstracts for relevance to the KQs. The titles and abstracts were screened independently by two reviewers. Inclusion at the title screening level was liberal; if a single reviewer believed an article might contain relevant information, the article was moved to the abstract level for further screening. When reviewing abstracts followed by the full text of articles, both reviewers had to agree on inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third expert member of the team (see Appendix C for screening forms). At random intervals during screening, quality checks by senior team members were performed to ensure that the eligibility criteria were applied consistently.

Quality (Risk of Bias) Assessment of Individual Studies

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

Answers of "Yes" were given a score of one, and answers of "No" or "Unclear" were given a score of zero. To simplify the presentation of the assessments of study quality for the grading of the strength of evidence, we combined the ratings of the five items into an overall rating of potential risk of bias as low, medium, or high. We used the assessment of the first three items (covering selection bias and performance/detection bias) as the starting point, with a cumulative score of three designated as low risk of bias, two or one as medium risk of bias, and zero as high risk of bias. The overall rating of risk of bias was downgraded if there was also a concern about either incomplete reporting or selective outcome reporting. When assessing the risk of bias, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing.

Data Synthesis

We reviewed primary studies, as defined by our inclusion criteria, as well as recent meta-analyses, and we performed de novo meta-analyses. The de novo meta-analyses included all studies that met our inclusion criteria. Prior to conducting meta-analyses, clinicians discussed differences in the study design and reporting to identify characteristics that would limit the clinical meaningfulness of pooled results, such as the variability in outcome definitions, type of contrast media used, and route of contrast media administration. Differences in these items either prevented the statistical pooling with meta-analysis or were used to stratify the meta-analysis estimates. Pooled risks were calculated using a random effects model using the method of DerSimonian and Laird.[16] Statistical heterogeneity was assessed using the I-squared statistic. When the I-squared value was greater than or equal to 50%, or the p-value was 0.2 or less, the clinicians were asked to re-evaluate the studies for clinical heterogeneity and decide if the meta-analysis should be reported despite statistical heterogeneity. After reviewing the available evidence on all of the comparisons of interventions for preventing CIN, we felt that the

heterogeneity across comparisons and the differences between reference groups were too great to support a network meta-analysis.

In many of the studies, the intervention group or the comparison group received more than one intervention. Therefore, we stratified the analyses according to the comparisons that were made, taking into consideration whether the intervention group or comparison group received more than one intervention. For example, we performed separate analyses for the following comparisons: N-acetylcysteine with intravenous saline versus intravenous saline with or without placebo; N-acetylcysteine with intravenous saline versus intravenous sodium bicarbonate; and N-acetylcysteine with intravenous sodium bicarbonate versus other interventions. The most common co-intervention was administration of fluids. We specified what type of fluids was given whenever that was part of the intervention. For the analyses of N-acetylcysteine, all of the studies included intravenous fluids as a co-intervention with N-acetylcysteine, so we could not do a network meta-analysis or meta-regression to assess the effect of the co-intervention.

We used Harbord's Modified Test for Small Study Effects to determine whether there was asymmetry in effect estimates when plotted against the standard error of the estimates, which can occur when publication bias exists.

Minimally Important Difference

To assess the clinical importance of differences in the incidence of CIN, a binary outcome, we followed guidance for selecting a minimally important difference based on the overall observed event rate in the studies.[17] Taking into consideration the potential effect of CIN on a patient's overall health and well-being, the clinical experts on our team decided that a relative risk reduction of 25% would be clinically important, which is consistent with the guidance suggesting a relative risk reduction of 20% to 30% in determining optimal information size.

Strength of the Body of Evidence

The team graded the strength of evidence on comparisons of interest for the key outcomes, focusing mainly on the incidence of CIN, for which the most evidence was available. We used the grading scheme recommended in the Methods Guide, and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect (Methods Guide).[18] Following the guidance of the GRADE Working Group,[17] we rated evidence as precise if the total number of patients exceeded an optimum information size, and the 95% confidence interval (CI) excluded a risk ratio of 1.0. We rated the evidence as imprecise if the 95% CI did not exclude the possibility of a clinically important benefit or harm (i.e., RR less than 0.75 or greater than 1.25) despite having an optimum information size. For the main outcome of interest, CIN, we used an optimum information size of 2000 based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative difference of 25%. For less frequent adverse outcomes, we used an optimum information size of 10,000 based on an expected 0.02 probability in the comparison group and a minimally important relative difference of 25%. We classified the strength of evidence pertaining to each comparison into four grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. If the magnitude of effect was very large, the strength of evidence could be upgraded.

Applicability

We considered elements of the PICOTS framework (Table 1) when evaluating the applicability of evidence to answer our Key Question as recommended in the Methods Guide.[18] This includes important population characteristics, treatment characteristics, and settings that may cause heterogeneity of treatment effects and limit applicability of the findings.

Results

Results of the Literature Search

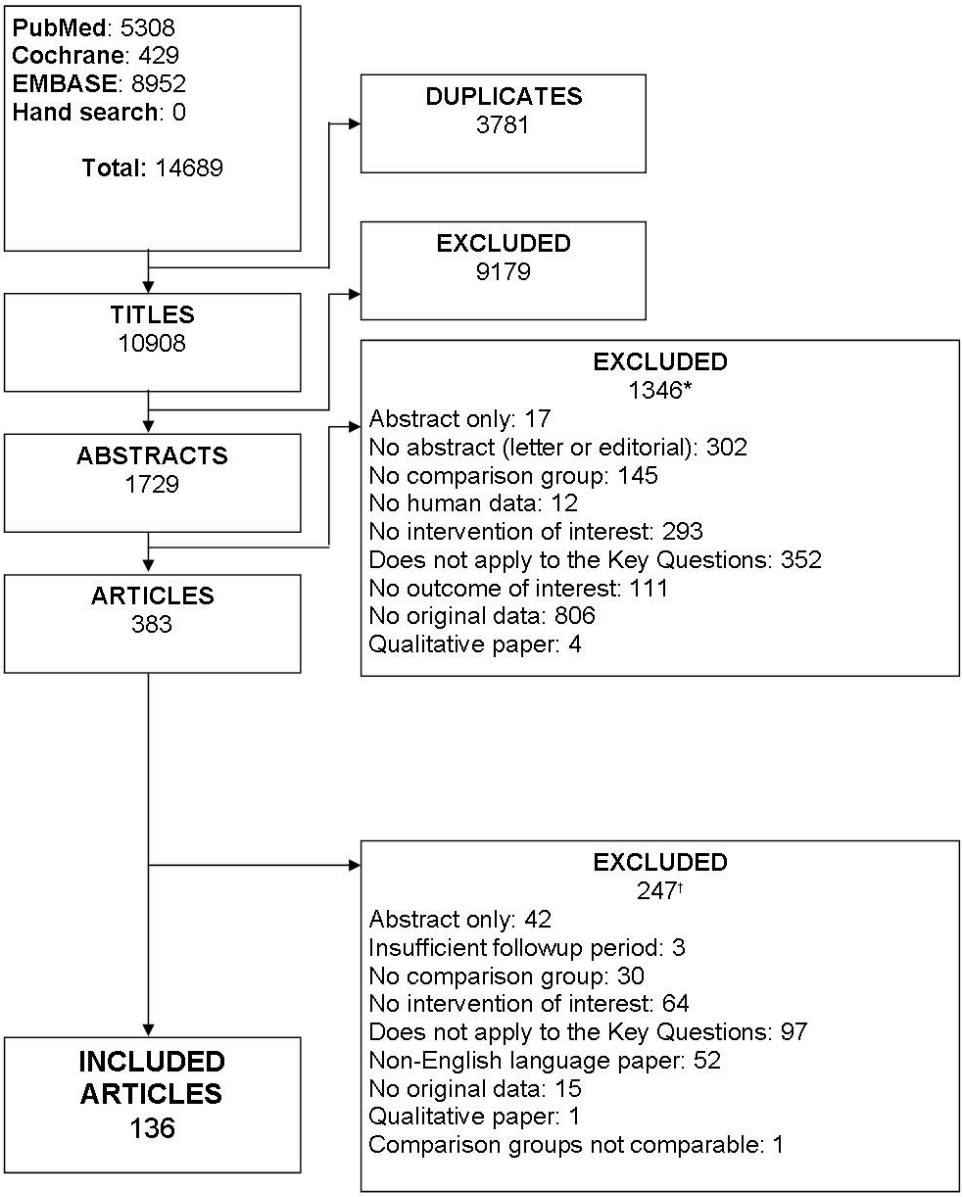
The literature search identified 10,908 unique citations, and we ultimately found 135 interventional studies that met the eligibility criteria (Figure 2 and Appendix D). None of the previous systematic reviews we found addressed the overall objectives of this review well enough to serve as the basis for an update instead of a comprehensive de novo review.

Key Question: In patients undergoing imaging studies requiring intravenous or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy (CIN), for the outcomes of incidence of CIN, chronic kidney disease (CKD), end stage renal disease (ESRD), mortality, and other adverse events?

Key Points

- The strength of evidence was low that high-dose N-acetylcysteine (> 1200 mg/day) was effective for the prevention of CIN when compared with intravenous saline; the overall pooled risk ratio (RR) for CIN was 0.70 (95% CI: 0.50 to 1.0), indicating a small, clinically important benefit for high dose N-acetylcysteine, with a number needed to treat of 21 (95% CI: 13 to 172).
- The strength of evidence was low that low-dose N-acetylcysteine (1200 mg/day or less) had a small effect on the risk of CIN when compared with intravenous saline; the overall pooled RR for CIN was 0.80 (95% CI: 0.60 to 0.90), indicating that the risk of CIN was decreased, but by an amount that tended not to be clinically important.
- The strength of evidence was low that intravenous sodium bicarbonate did not differ from intravenous saline in the risk of CIN; the overall pooled RR for CIN was 0.8 (95% CI: 0.5 to 1.2), with a point estimate indicating a clinically unimportant difference, and a wide CI that only ruled out an important increase in CIN without ruling out the possibility of an important decrease in CIN.
- The strength of the evidence was insufficient about whether N-acetylcysteine differed from sodium bicarbonate in the prevention of CIN.
- The strength of the evidence was moderate that statins produced a small to medium reduction in CIN when compared to intravenous saline alone for the prevention of CIN; the overall pooled RR was 0.5 (95% CI: 0.4 to 0.8) with a number needed to treat of 45 (95% CI: 30-217).
- The evidence was insufficient evidence to determine whether adenosine antagonists are effective at preventing CIN.
- The strength of the evidence was low that hemodialysis does not reduce CIN and may even be harmful (RR 1.4; 95% CI: 0.9 to 2.2).

Figure 2. Screening flow



* Sum of excluded abstracts exceeds 1346 because abstracts could be excluded for multiple reasons.
† Sum of excluded articles exceeds 247 because articles could be excluded for multiple reasons.

N-acetylcysteine plus Intravenous Saline versus Intravenous Saline with or without Placebo

Although the pathophysiology of CIN is not completely understood, it is thought that renal medullary ischemia and direct toxicity to renal tubules by oxygen free radicals may contribute. N-acetylcysteine is a direct scavenger of free radicals and improves blood flow through nitric oxide–mediated pathways, which results in vasodilation, so both the antioxidant and vasodilatory properties of N-acetylcysteine are thought to provide protection against CIN.

Although early studies showed benefits of N-acetylcysteine in patients receiving HOCM or LOCM, subsequent studies and meta-analyses offer mixed results concerning the efficacy of N-acetylcysteine for prevention of CIN. It is possible that the effectiveness of N-acetylcysteine depends on the administered dose and route of administration of N-acetylcysteine, the osmolality of contrast media and its route of administration, and study population characteristics.

Study Characteristics

A total of 63 studies were identified that compared N-acetylcysteine to intravenous saline. Of these studies, 57 reported on CIN directly, and six reported on serum creatinine or GFR without reporting the incidence of CIN. Of the 57 studies reporting on CIN directly, we found 44 RCTs of N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo, published between 2002 and 2013, which we could include in a meta-analysis. The number of patients in each trial ranged from 40 to 499, and the study populations across the studies were very heterogeneous. Study patients had renal dysfunction at baseline (defined as baseline serum creatinine greater than 1.2 mg/dl) in 28 studies.[19-46] Sixteen studies included patients with cardiac risk factors and a general population which included a mixture of patients with and without renal dysfunction.[47-62]

Across all of the studies, a total of 3207 patients received intravenous saline with or without placebo, and 3185 patients received N-acetylcysteine. The route and dose of N-acetylcysteine varied between studies. A total of 32 studies administered N-acetylcysteine orally,[21-25, 27, 28, 30-41, 43-46, 49, 51-53, 55, 57, 58, 60, 62] 11 studies administered N-acetylcysteine intravenous,[19, 20, 26, 29, 42, 47, 48, 50, 54, 59, 61] and one study used a combination of intravenous and oral N-acetylcysteine.[56] Thirty studies[19-25, 27-30, 34-36, 38-41, 43, 44, 46, 47, 49, 52, 55, 57, 58, 60, 61] used a low dose of N-acetylcysteine (1200 mg/day or less), and 13 studies used a higher dose (greater than 1200 mg/day).[26, 31-33, 37, 42, 45, 48, 50, 51, 53, 54, 59] One study had one arm with low-dose N-acetylcysteine, and a second arm with high-dose N-acetylcysteine, and a control arm that received a placebo in intravenous saline.[56]

Contrast media was administered intravenous in six studies[26, 41, 44, 47, 55, 60] and intra-arterial in 38 studies. Five studies used IOCM,[22, 35, 42, 50, 55] 33 used LOCM, five used either IOCM or LOCM[21, 27, 38, 58, 62] and one used IOCM, LOCM, or HOCM.[45]

Variation existed in the protocols for giving fluids, with studies using 0.45% saline; normal saline; 5% dextrose in normal saline, or alone; or Ringer's lactate solutions. Varying volumes were administered in the studies. The studies used three definitions of CIN: 0.5 mg/dl absolute increase, 25 percent increase in serum creatinine, or a combination of both. All of the studies except one measured the change in serum creatinine between 48 and72 hours. One[59] measured the change in serum creatinine at 24 hours after contrast media administration (Appendix E, Evidence Table 1-3, 4).

Contrast-induced Nephropathy

The 44 RCTs comparing N-acetylcysteine plus intravenous saline to intravenous saline with or without placebo in the reduction of CIN showed a range of results, including: five reported a clinically important reduction in the risk of CIN, 20 reported a clinically important reduction in the risk of CIN that was not statistically significant, five did not show a clinically important reduction in the risk of CIN, 11 did not show a clinically important increased risk of CIN, two showed a clinically important increased risk of CIN that was not statistically significant, and one showed a clinically and statistically significant increased risk of CIN.

The pooled risk ratio of CIN, using a random effects model, for high-dose N-acetylcysteine (> 1200 mg/day) was 0.70 (95% CI: 0.50 to 1.0; 12 studies), indicating that, on average, the benefit is at a level consistent with a clinically important reduction in CIN; however the CI did not rule out an unimportant difference (Figure 3). This is consistent with a number needed to treat of 21 (95% CI: 13 to 172. There was moderate statistical heterogeneity across studies with an I^2 of 37.3%. The RR for CIN from the 13 studies using intra-arterial contrast media and high-dose N-acetylcysteine was 0.70 (95% CI: 0.5 to 1.0), while only one study used intravenous contrast media and high-dose N-acetylcysteine and the results were too imprecise to draw conclusions (RR 0.30; 95% CI: 0.1 to 1.10). The strength of the evidence was low that high-dose N-acetylcysteine was more effective at preventing CIN than a placebo or usual care (Table 3).

The pooled RR for CIN using a random effects model for low-dose N-acetylcysteine (1200 mg/day or less) was 0.80 (95% CI: 0.60 to 0.90; 30 studies), indicating that, on average, the small difference is at a level consistent with a clinically unimportant reduction in CIN (Figure 4). The statistical heterogeneity of the studies was low, with an I-squared (I^2) of 0.5%. The RR for the five studies using intravenous contrast media and low-dose N-acetylcysteine was 0.70, but in this small subset of studies the 95% CI was so wide that we cannot rule out a clinically important increased risk (95% CI: 0.3 to 1.4; 5 studies). For 26 studies using intra-arterial contrast media and low-dose N-acetylcysteine, the RR was 0.80 (95% CI: 0.6 to 0.90) indicating that, on average, the benefit is at a level consistent with a clinically unimportant reduction in CIN. Using Harbord's Modified Test for Small Study Effects, we did not find evidence of asymmetry in results by study precision (bias coefficient of -0.30, standard error of 0.43, p=0.49). Overall, the strength of the evidence was low about the small effect of low-dose N-acetylcysteine in preventing CIN compared with a placebo or usual care (Table 3).

We performed stratification analyses to investigate the influence of contrast media osmolality on the effect of N-acetylcysteine. The pooled risk ratio of CIN, using a random effects model, for 5 studies using LOCM was 0.70 (95% CI: 0.6 to 0.8) indicating that, on average, the difference is consistent with a clinically important reduction in CIN with N-acetylcysteine in patients receiving LOCM, but the CI does not rule out a clinically unimportant difference. The statistical heterogeneity across studies was low, with an I^2 of 14.2 percent. The pooled RR for CIN from five studies of N-acetylcysteine using IOCM was 1.20 (95% CI: 0.9 to 1.8), The confidence interval was wide enough for N-acetylcysteine when IOCM was used to suggest possible harm without any indication of a clinically important benefit (Figure 5). The pooled RR for CIN from four studies of N-acetylcysteine using a mixture of IOCM and LOCM was 0.80 (95% CI: 0.4 to1.5), with a CI so wide that we cannot rule out either a clinically important reduction in risk or a clinically important increase in risk. The estimates of effect are remarkably stable across different types of studies with a 20 to 30 percent reduction which is near the edge of clinical significance. The variation is mainly in the confidence intervals, which is likely due to variation

in the number of people in the different studies. We used Harbord's Modified Test for Small Study Effects and found no evidence of asymmetry in results by study precision (bias coefficient of -0.66, standard error of 0.78, p=0.42)

We also performed stratification analyses to investigate the influence of the route of N-acetylcysteine administration. The pooled RR for CIN, using a random effects model, for patients who received oral N-acetylcysteine was 0.70 (95% CI: 0.6 to 0.9), indicating that, on average, the difference was clinically important, but the CI does not rule out a clinically unimportant reduction in risk. The pooled RR for CIN for patients who received intravenous N-acetylcysteine was 0.90 (95% CI: 0.7 to 1.1), indicating that the difference is not clinically important (Figure 6).

Our sensitivity analysis, which removed one study at a time, did not show any significant impact on the estimated effect of N-acetylcysteine. There was no trend in the effect size by year of the study publication (Figure 3). Thirteen of the 57 studies reporting on CIN were not included in the meta-analyses for a variety of reasons, including missing data, dosage differences, inclusion criteria difference (see Appendix E, Evidence Table 5). In addition to the studies that reported on the incidence of CIN, we found six studies that reported on changes in serum creatinine (Appendix E, Evidence Table 6) and/or GFR (Appendix E, Evidence Table 7) without reporting on the incidence of CIN. In those six studies, the mean change in serum creatinine or GFR did not differ enough between groups to meet the definition of CIN.

When we examined how the RR estimates varied according to baseline characteristics of the study population, we did not observe any meaningful difference by age, baseline renal function, or the presence or absence of diabetes mellitus.

Other Outcomes

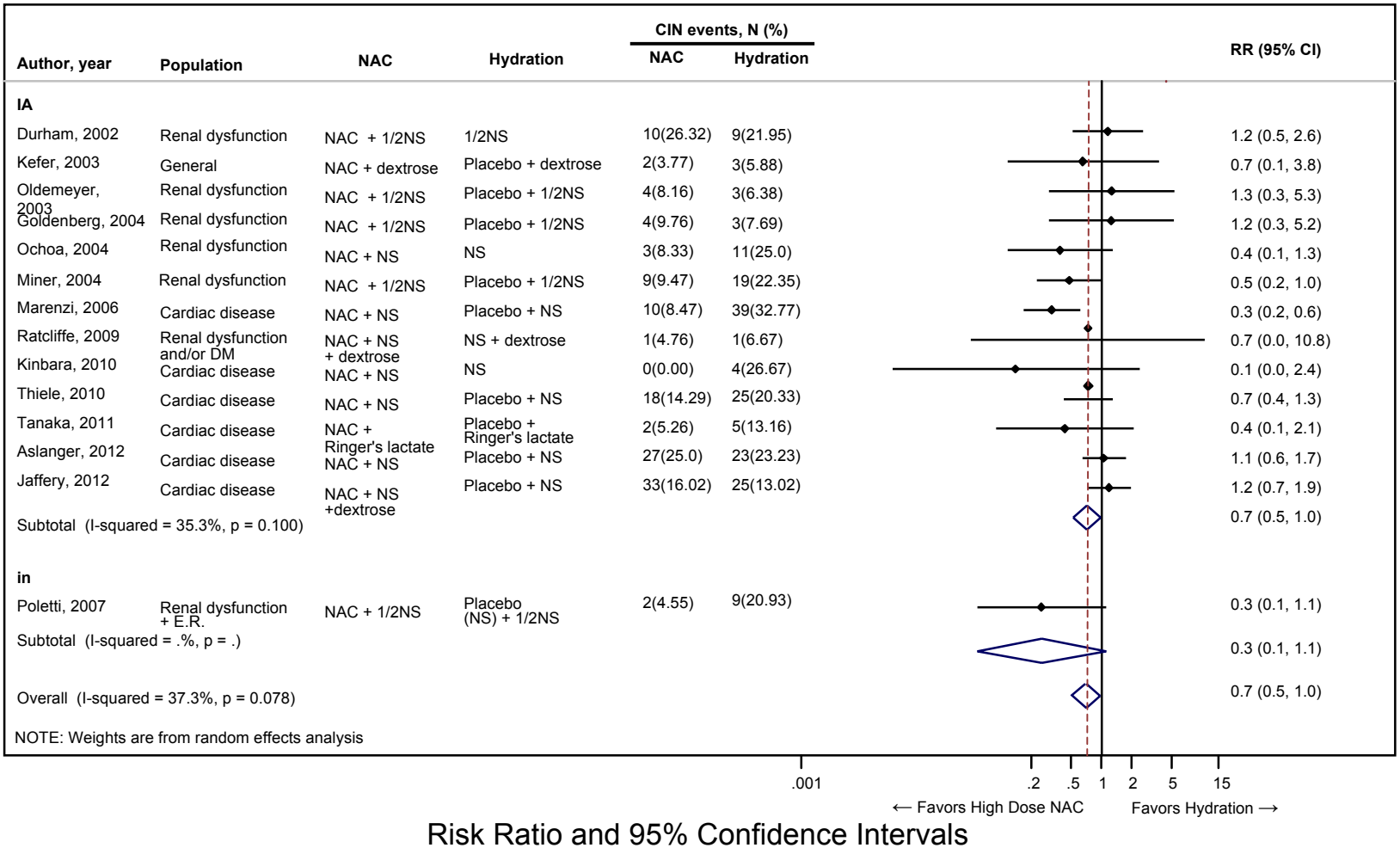
Of the 63 studies investigating development of CIN when comparing N-acetylcysteine plus intravenous saline against a placebo with or without intravenous saline, 43 also included data on secondary outcomes. Twenty-three reported data on patients' need for renal replacement therapy (RRT),[20, 22, 25, 28, 29, 31, 33, 37-40, 43, 47, 56-58, 63-69] seven reported data on cardiac events,[23, 25, 31, 32, 54, 64, 68]14 of those 30 studies reported data on mortality,[20, 22, 28, 31, 47, 50, 54, 56-58, 61, 63, 65, 69] and eight reported data on length of hospitalization (Appendix E, Evidence Table 8).[20, 33, 36, 50, 51, 61, 65, 68]

The strength of the evidence was low that N-acetylcysteine plus intravenous saline does not differ from placebo with or without intravenous saline at decreasing the need for RRT, cardiac events, or the length of hospitalization. (Table 3, Appendix E, Evidence Table 8). The studies in each of these outcome groups had medium study limitations, were direct, and consistent in the direction of impact of N-acetylcysteine. All were downgraded for imprecision. One study, Marenzi, et al.,2006,[56]reported a statistically significant and clinically important difference in mortality between the placebo arm and the N-acetylcysteine arms, with more in-hospital deaths in the placebo arm (placebo: 13/119 (11%); standard dose N-acetylcysteine: 5/115 (4%); high dose N-acetylcysteine: 3/118 (3%), p=0.007).[56] Two studies reported significant findings for length of hospitalization. Hsu, et al., 2007[68] showed a statistically significant and clinically important reduction in length of hospitalization in the N-acetylcysteine arm (placebo: mean 8.1 days (standard deviation [SD] 4.1); low dose N-acetylcysteine: mean 5.2 days [SD 1.5], p=0.04).[68] Kay, et al., 2003[36] also showed a statistically significant reduction in length of hospitalization in the N-acetylcysteine arm, but the difference was not clinically important (placebo: mean 3.9 days (SD 2.0); low dose N-acetylcysteine: mean 3.4 days (SD 0.9), p=0.02).[36] No statistically significant differences were reported for cardiac events.

The strength of the evidence was insufficient to determine whether any difference in mortality exists between N-acetylcysteine plus intravenous saline compared with placebo with or without intravenous saline. The studies reporting on mortality had medium study limitations, and were inconsistent and imprecise regarding the effectiveness of N-acetylcysteine (Table 3, Appendix E, Evidence Table 8).

Adverse events were mentioned in 26 studies. Data was only recorded if a specific adverse event was reported or the study reported no adverse events (Appendix E, Evidence Table 9). Adverse events were not reported in a standardized manner and rarely were they analyzed in these studies, so we were not able to draw any firm conclusions about whether the incidence of adverse events differed between N-acetylcysteine with intravenous saline versus placebo without or without intravenous saline.

Figure 3. Meta-analysis of high-dose* N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo for the prevention of contrast-induced nephropathy.



%=percent; 1/2NS=0.45% saline; CI=confidence interval; CIN=contrast-induced nephropathy; DM=diabetes mellitus; ER=emergency room; IA=intra-arterial; IV=intravenous; N=sample size; NAC=N-acetylcysteine; NS=normal saline; P=p-value; RR=risk ratio

*High dose NAC refers to studies that administered more than 1200mg NAC daily to participants

Figure 4. Meta-analysis of low dose* N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo for the prevention of contrast-induced nephropathy.

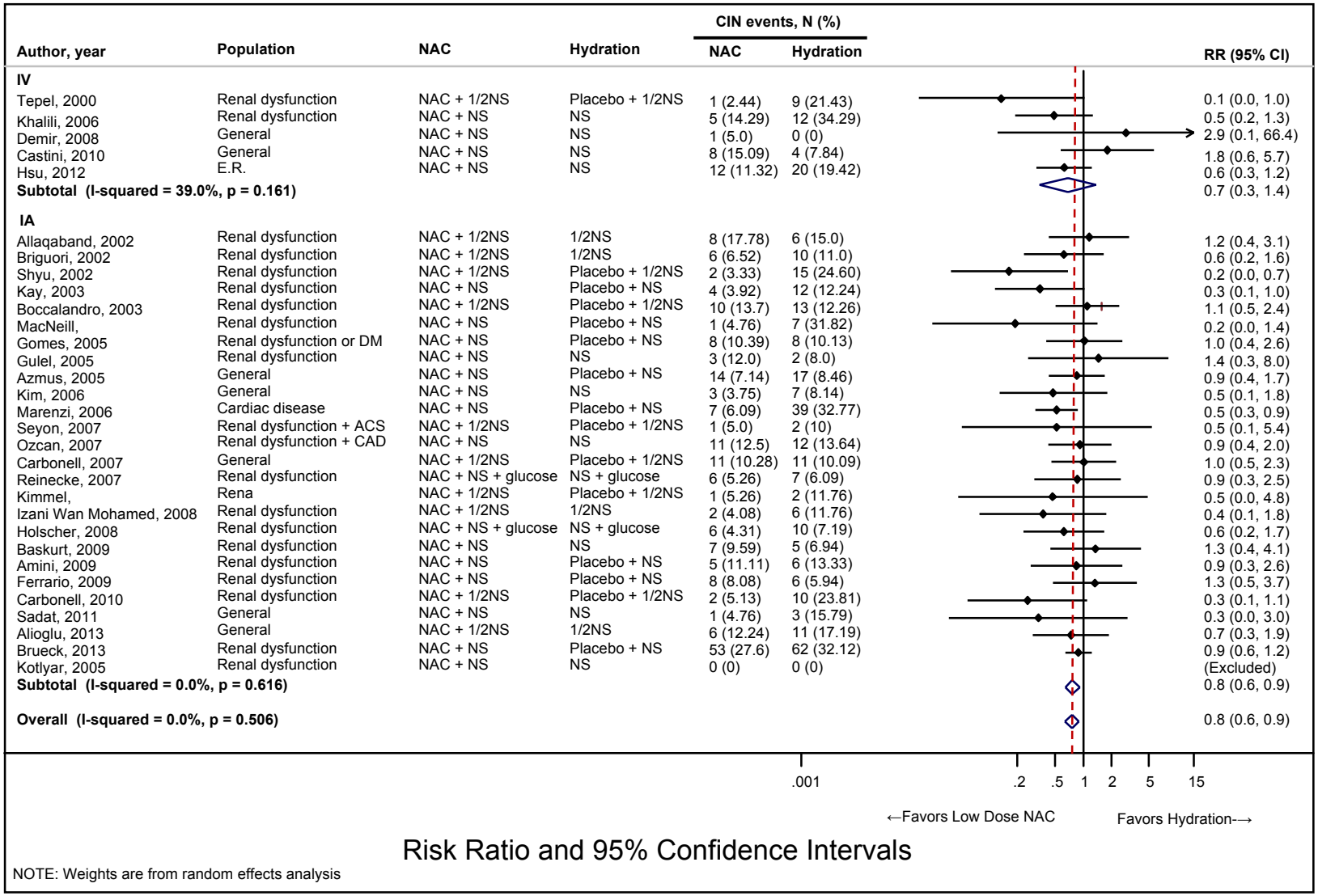
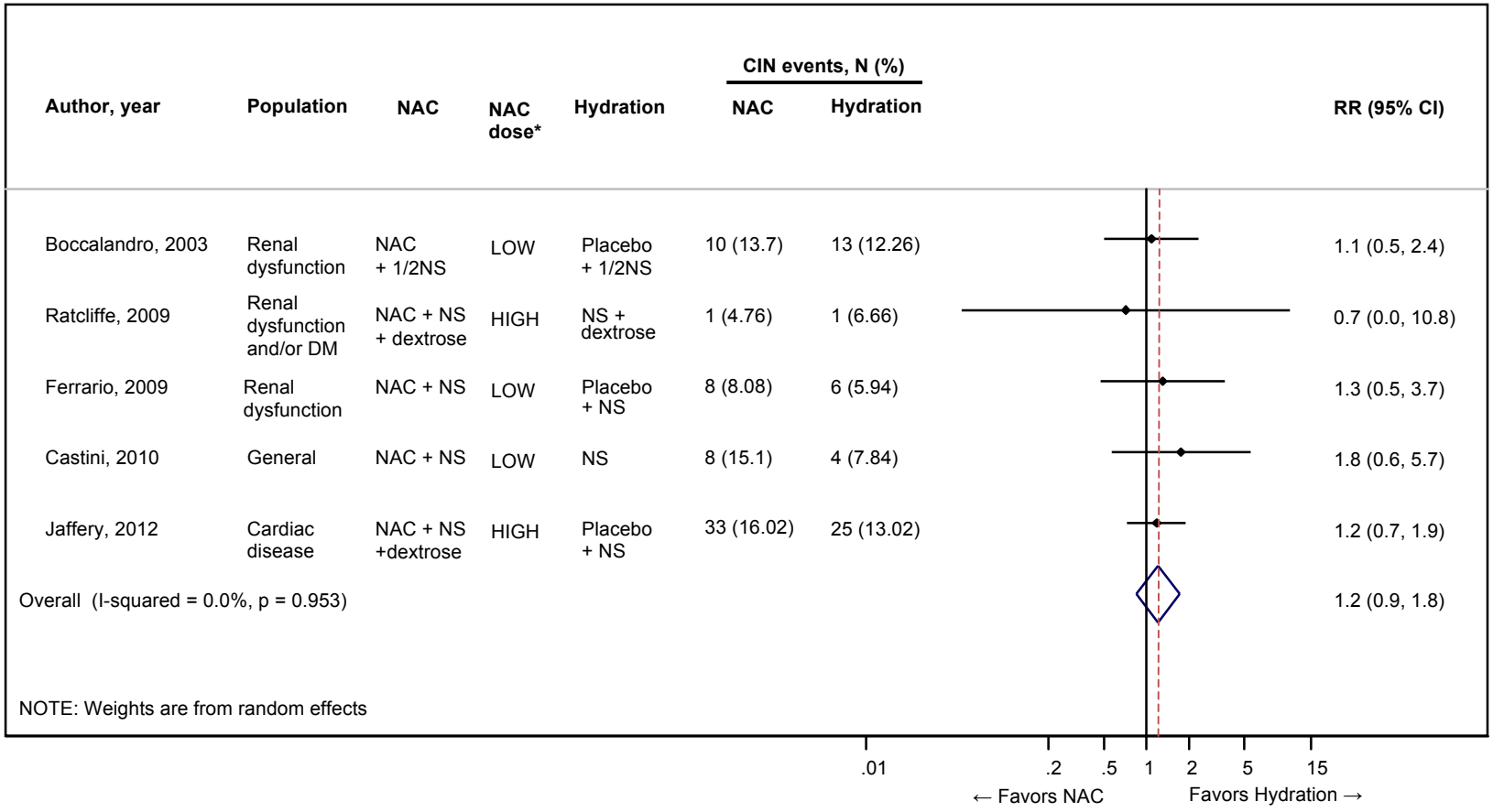


Figure 4. Meta-analysis of low dose* N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo for the prevention of contrast-induced nephropathy (continued).

%=percent; 1/2NS=0.45% saline; ACS=acute coronary syndrome; CAD=coronary artery disease; CI=confidence interval; CIN=contrast-induced nephropathy; DM=diabetes mellitus; ER=emergency room; IA=intra-arterial; IV=intravenous; N=sample size; NAC=N-acetylcysteine; NS=normal saline; P=p-value; RR=risk ratio

*Low dose NAC refers to studies that administered 1200mg or less NAC daily to participants

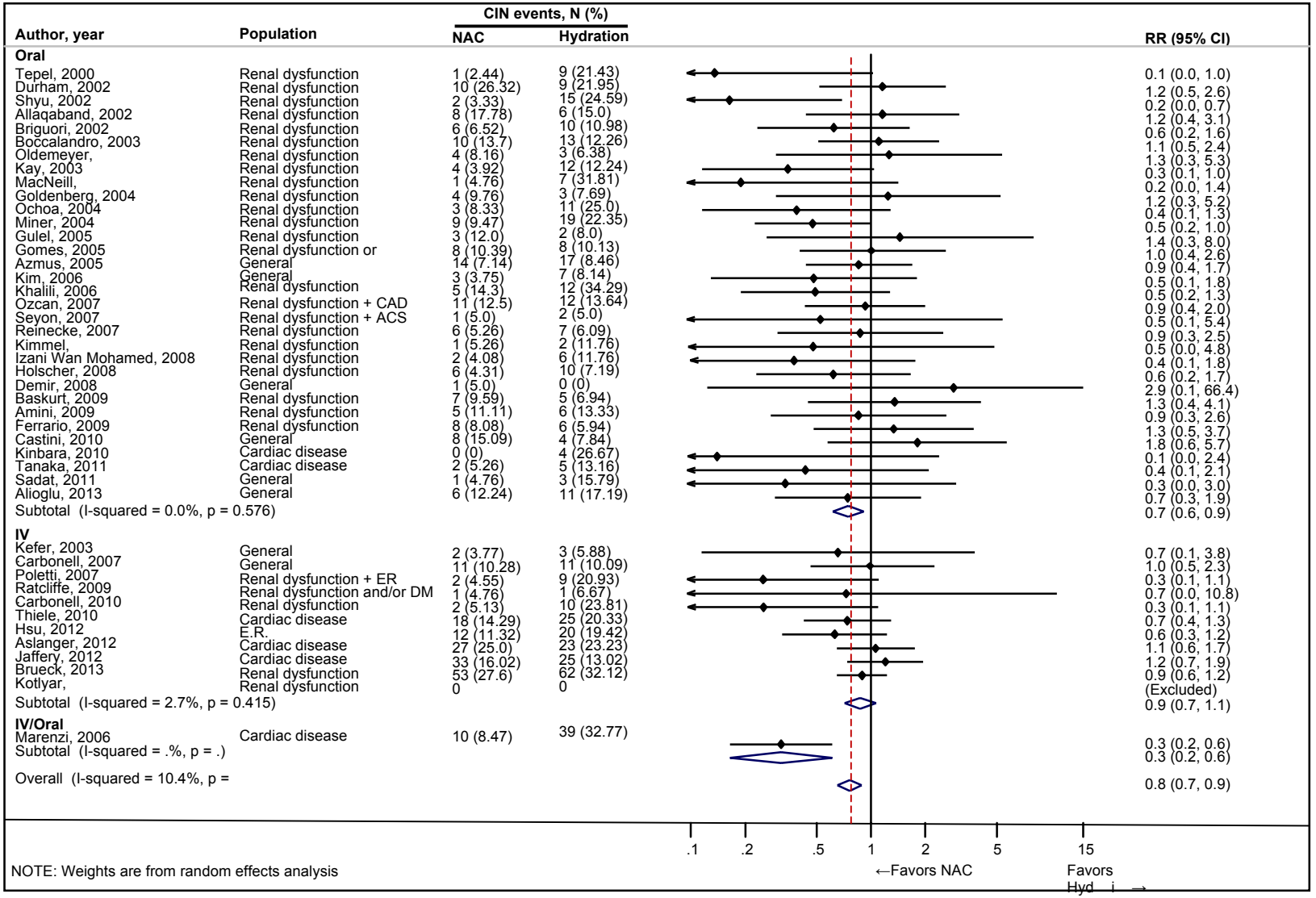
Figure 5. Meta-analysis of N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo for the prevention of contrast-induced nephropathy when iso-osmolar contrast is used.



%=percent; 1/2NS=0.45% saline; CI=confidence interval; CIN=contrast-induced nephropathy; DM=diabetes mellitus; ER=emergency room; N=sample size; NAC=N-acetylcysteine; NS=normal saline; P=p-value; RR=risk ratio

*Low dose NAC refers to studies that administered 1200mg or less NAC daily to participants. High dose NAC refers to studies that administered more than 1200mg NAC daily.

Figure 6. Meta-analysis of oral vs intravenous route of N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo for the prevention of contrast-induced nephropathy.



Risk Ratio and 95% Confidence Intervals

Figure 6. Meta-analysis of oral vs intravenous route of N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo for the prevention of contrast-induced nephropathy(continued).

%=percent; 1/2NS=0.45% saline; CI=confidence interval; CIN=contrast-induced nephropathy; DM=diabetes mellitus; ER=emergency room; IA=intra-arterial; IV=intravenous; N=sample size; NAC=N-acetylcysteine; NS=normal saline; P=p-value; RR=risk ratio

Table 3. Summary of the strength of evidence: N-acetylcysteine plus intravenous saline versus intravenous saline with or without placebo.

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of outcomes
Development of CIN (high-dose NAC)	RCT: 14 (2239)	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that high-dose NAC with IV saline has a clinically important benefit in preventing CIN compared with IV saline without NAC
Development of CIN (low-dose NAC)	RCT: 31 (5428)	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that low-dose NAC with IV saline has a small clinically unimportant benefit in preventing CIN compared with IV saline without NAC
Development of CIN (all studies)	RCT: 55 (10,923)	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that, overall, NAC with IV saline has a small clinically unimportant benefit in preventing CIN compared with IV saline without NAC
Need for RRT	RCT: 23 (6774)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC with IV saline does not differ from IV saline alone in preventing need for RRT
Cardiac events	RCT: 7 (1092)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC with IV saline does not differ from IV saline alone in preventing cardiac events
Mortality	RCT: 14 (5294)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence regarding effect of NAC with IV saline on preventing mortality compared with IV saline alone
Hospitalization, length of stay	RCT: 8 (877)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC with IV saline does not differ from IV saline alone in reducing length of hospitalization

CIN=contrast-induced nephropathy; IV = intravenous; N=sample size; NA=not available; NAC=N-acetylcysteine; RCT=randomized controlled trial; RRT=renal replacement therapy

Intravenous Sodium Bicarbonate versus Intravenous Saline

A major underlying hypothesis for using intravenous sodium bicarbonate to prevent CIN is that the alkalinization of tubular fluid diminishes the production of free oxygen radicals, which may play a role in the etiology of CIN.[70] Prior meta-analyses showed a mixed effect for intravenous sodium bicarbonate, with some demonstrating benefit for intravenous sodium bicarbonate[71, 72] while other meta-analyses were inconclusive.[73]

Study characteristics

Twenty-three articles were identified that compared intravenous sodium bicarbonate to intravenous saline. Thirteen RCTs[25, 42, 55, 74-83] published between 2004 and 2013 were included in the meta-analysis.

In these studies, CIN was defined in three ways (Appendix E, Evidence Table 1-3, 10): five defined it as a 25 percent or more increase in serum creatinine, one defined it as a 0.5 mg/dl or more increase in serum creatinine, and seven defined it as either a 25 percent rise or 0.5 mg/dl increase in serum creatinine.

A total of 2283 patients were included in these studies; they included ages between 40 and 87. Six[25, 55, 77, 79, 81, 82] of the 13 studies included general patients who underwent diagnostic or interventional cardiac procedures, four included patients with diabetes mellitus,[42, 74, 76, 83] one selectively included patients with CKD,[78] and another included patients with stable renal disease.[80] The route of contrast media administration was intra-arterial in eleven studies,[25, 42, 55, 75-81, 83] intravenous in one study,[74] and both intravenous and intra-arterial in one study.[74, 82] Two studies used IOCM[55, 76] and the other eleven used LOCM. (Appendix E, Evidence Table 1-3, 10).

Contrast-induced Nephropathy

Six studies concluded that intravenous sodium bicarbonate administration reduced the incidence of CIN when compared with intravenous saline, while seven reported no difference in the incidence of CIN between the intravenous sodium bicarbonate and intravenous saline intervention arms. The meta-analysis indicated that administration of intravenous sodium bicarbonate did not differ from intravenous saline in the risk of CIN (RR 0.80; 95% CI: 0.5 to 1.2), with a point estimate indicating a clinically unimportant difference, and a wide CI that only ruled out an important increase in CIN without ruling out the possibility of an important reduction in CIN. The strength of evidence was low for this conclusion (Table 4). The studies reporting on CIN had medium study limitations with some inconsistency.

Overall, the studies had moderate heterogeneity, with an I^2 of 48 percent (p=0.028) (Figure 7). Using Harbord's Modified Test for Small Study Effects, we found no evidence of asymmetry in the distribution of results by study precision (bias coefficient of -1.08, standard error of 1.21, p = 0.39).

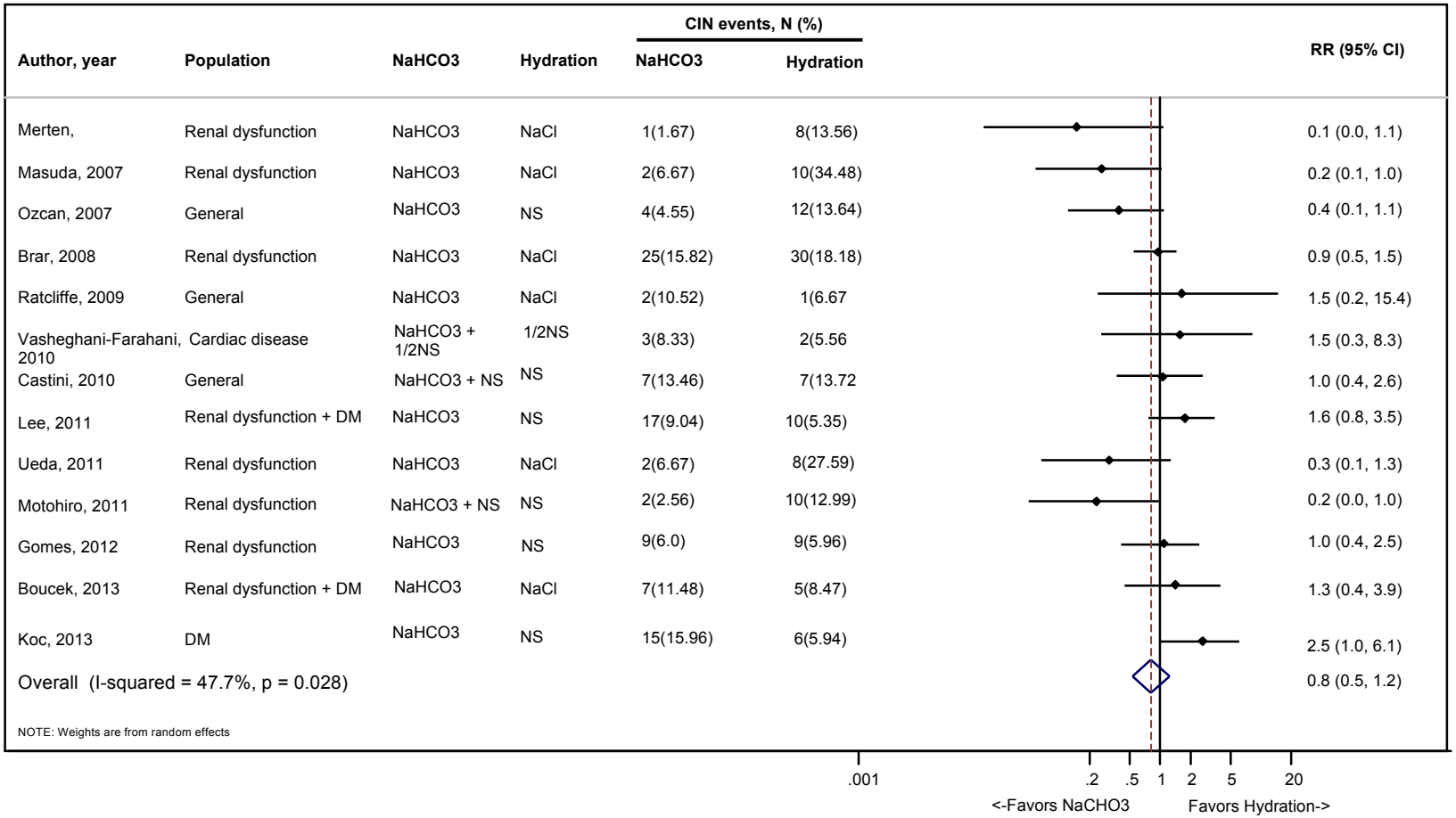
Eleven of the 23 studies reporting on CIN were not included in the meta-analysis for a variety of reasons (see Appendix E, Evidence Table 11). One study did not report on CIN as an outcome but did report on serum creatinine. The mean change in serum creatinine from baseline did not meet any definition of CIN (Appendix E, Evidence Table 12).

Other Outcomes

Of the 23 studies that compared the risk of CIN between intravenous sodium bicarbonate and intravenous saline, nine studies included data on secondary outcomes. Out of these nine studies, eight reported data on participants' need for RRT,[25, 42, 74-77, 80, 81] two reported data on cardiac events,[25, 76] five studies reported data on mortality[74-76, 78, 80, 81] two reported data on length of hospitalization.[74, 75, 78] No statistically significant differences were reported for any of the secondary outcomes (Appendix E; Evidence Table 6b, 7e-i).[55, 79, 82, 83]The overall strength of the evidence was low that mortality and the need for RRT do not differ between intravenous sodium bicarbonate and intravenous saline. The studies addressing the need for RRT and mortality had medium study limitations, were consistent in the direction of effect, and imprecise due to wide confidence intervals and small study populations. The evidence was insufficient to determine whether cardiac events or length of hospitalization differ between intravenous sodium bicarbonate and intravenous saline (Table 4; Appendix E, Evidence Table 13).

Adverse events were reported in eight studies. Data was only recorded if specific adverse events were reported or the study reported no adverse events (Appendix E, Evidence Table 14). Adverse events were not reported in a standardized manner and rarely were they analyzed in these studies, so we were not able to draw any firm conclusions about whether the incidence of adverse events differed between intravenous sodium bicarbonate and intravenous saline..

Figure 7. Meta-analysis of intravenous sodium bicarbonate versus intravenous saline for the prevention of contrast-induced nephropathy.



%=percent; 1/2NS=0.45% saline; CI=confidence interval; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; DM=diabetes mellitus; N=sample size; NAC=N-

Table 4. Summary of the strength of evidence: intravenous sodium bicarbonate versus intravenous saline.

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN	RCT: 14 (2548)	Medium	Direct	Inconsistent	Precise*	Low	Low strength of evidence that IV sodium bicarbonate did not differ from IV saline in the risk of CIN
Need for RRT	RCT: 7 (1604)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that the need for RRT did not differ between IV sodium bicarbonate and IV saline
Cardiac events	RCT: 2 (642)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether cardiac events differ between IV sodium bicarbonate and IV saline
Mortality	RCT: 5 (1185)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that mortality rates did not differ between IV sodium bicarbonate and IV saline
Hospitalization, length of stay	RCT: 2 (421)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether length of hospitalization differs between IV sodium bicarbonate and IV saline

* The results were precise enough to rule out a clinically important increase in CIN with IV sodium bicarbonate.

CIN=contrast-induced nephropathy; IV=intravenous; N=sample size; NA=not available; RCT=randomized controlled trial; RRT=renal replacement therapy

N-acetylcysteine versus Sodium Bicarbonate

In previous sections, we briefly explained the physiologic basis for studying the use of N-acetylcysteine or intravenous sodium bicarbonate to prevent CIN, and we summarized the evidence on the effectiveness of each of these two interventions compared with intravenous fluids alone. In this part of the analysis, we looked for evidence on head-to-head comparisons of these two interventions.

Study Characteristics

We found four RCTs [25, 42, 55, 84] comparing the effectiveness of N-acetylcysteine plus intravenous saline against intravenous sodium bicarbonate in preventing CIN. In these studies, the CIN outcome was defined two ways: defined as an increase in serum creatinine of at least 25 percent from baseline or an increase in serum creatinine of at least 0.5 mg/dL[25, 85] or as an increase of at least 25 percent in serum creatinine from baseline.[42, 55, 84]

The studies had a total follow-up period of 48 hours to 7 days; the outcomes of CIN were reported at 48 hours,[25, 85] at 48 to 72 hours,[84] at 24, 48 and 120 hours (5 days),[55],(personal communication with Diego Castini, April 28, 2014), and 24, 48, and 168 hours (7 days).[42] The study population for three of the RCTs included only individuals with renal dysfunction.[25, 55, 84] The patients in the fourth RCT[42] had either kidney dysfunction or diabetes mellitus. The contrast media was delivered intra-arterial in all of the RCTs, and was given only for diagnostic and/or interventional coronary procedures in three of the RCTs. The patients in the fourth RCT underwent cardiac catheterization or another major arteriographic procedure.[84] (Appendix E, Evidence Tables 1-3, 15).[85]

All studies compared N-acetylcysteine plus intravenous saline (sometimes in 5% dextrose in water (D5W)) with intravenous sodium bicarbonate. In all studies, intravenous sodium bicarbonate and intravenous normal saline were given at 1 ml/kg/hour or at 3 ml/kg/hour before and after contrast media administration, but not always at the same rate. The timing of the intravenous sodium bicarbonate infusion varied between one to six hours before contrast administration, and from six to 12 hours post-contrast administration. The timing of the intravenous normal saline infusion varied between one and 12 hours before contrast administration, and between six and 12 hours after contrast administration. One study used intravenous N-acetylcysteine 1200 mg one hour before the intervention followed by 1200 mg of oral N-acetylcysteine twice daily for 48 hours after the intervention.[42] One study[84] did not specify whether the route of administration of N-acetylcysteine was oral or intravenous, but most likely it was oral N-acetylcysteine (600 mg twice daily on the day before and on the day of the procedure). The other two RCTs used 600 mg of oral N-acetylcysteine twice daily on the day before and the day of the procedure.[25, 55] Two of the RCTs used IOCM[42, 55] and two RCTs used LOCM (Appendix E, Evidence Tables 1-3, 15).[25, 84] Two of the studies had medium risk of bias,[55, 84] and three studies had a high risk of bias.[25, 42, 85]Conclusions did not differ based on study limitations. These studies were published from 2007 to 2013.

Contrast-induced Nephropathy

The incidence of CIN in the intravenous sodium bicarbonate groups ranged from 4.5 to 35.7 percent and from 4.7 to 15.8 percent in the N-acetylcysteine plus intravenous saline groups. Two of the RCTs favored intravenous sodium bicarbonate and two favored N-acetylcysteine plus

intravenous saline, although one study had very few CIN events (one CIN event in one group and two in the other group).[42] (Appendix E, Evidence Table 16).

The overall pooled RR for CIN in the RCTs comparing intravenous sodium bicarbonate with the combination of N-acetylcysteine and intravenous saline, using a random effects model, was 0.93 (95% CI: 0.40 to 2.1). The point estimate of the RR indicates a very small decrease in risk with sodium bicarbonate that was less than clinically important. The confidence interval was too wide to rule out the possibility of either an important decrease or important increase in risk. The studies were inconsistent, and had moderate heterogeneity, with an I^2 of 49.4 percent (Figure 8). The Harbord's Modified Test for Small Study Effects did not show evidence of asymmetry in results by study precision (bias coefficient of 0.20, standard error of 1.79, p=0.92). We concluded that the strength of the evidence was insufficient to support a conclusion about the comparative effectiveness of these two interventions in the ability to prevent CIN (Table 5; Appendix E, Evidence Table 16).

Limitations of this comparison included the small number of studies, the varying regimens of fluid administration and N-acetylcysteine dosing, and the variations in follow-up time. Four of the studies were exclusively in individuals with kidney disease (a population at higher risk for CIN), although the inclusion criteria were not exactly the same across all studies. One of the RCTs was conducted in individuals with either kidney dysfunction or diabetes mellitus. A potential concern in the Ratcliffe study is that only 66% of participants completed the study.[42]

Other Outcomes

Of the five studies that compared N-acetylcysteine plus intravenous saline with intravenous sodium bicarbonate for the development of CIN, secondary outcomes were only occasionally reported. Ozcan, et al.[25] reported that one of 88 patients in the intravenous sodium bicarbonate group required dialysis by 48 hours after contrast administration, but no patient in the N-acetylcysteine plus saline group required dialysis during this period (p value was not reported). There were no episodes of congestive heart failure in either arm. No participants died or required dialysis during the time period of the study in the Castini trial.[55] Heguilen et al.[84] reported no episodes of congestive heart failure, although seven patients were lost to follow-up. Length of hospital stay was not mentioned in any of the studies (Appendix E, Evidence Table 17). Insufficient evidence exists to support firm conclusions about the comparative effects of N-acetylcysteine versus sodium bicarbonate for the outcomes of need for RRT, cardiac events, mortality, or length of hospitalization.

Adverse events were reported in all studies. Data was recorded if specific adverse events were reported or the study reported no adverse events (Appendix E, Evidence Table 18). Adverse events were not reported in a standardized manner, and rarely were they analyzed in these studies, so we were not able to draw any firm conclusions about whether the incidence of adverse events differed between N-acetylcysteine with intravenous saline versus intravenous sodium bicarbonate.

Figure 8. Meta-analysis of N-acetylcysteine versus sodium bicarbonate for the prevention of contrast-induced nephropathy.

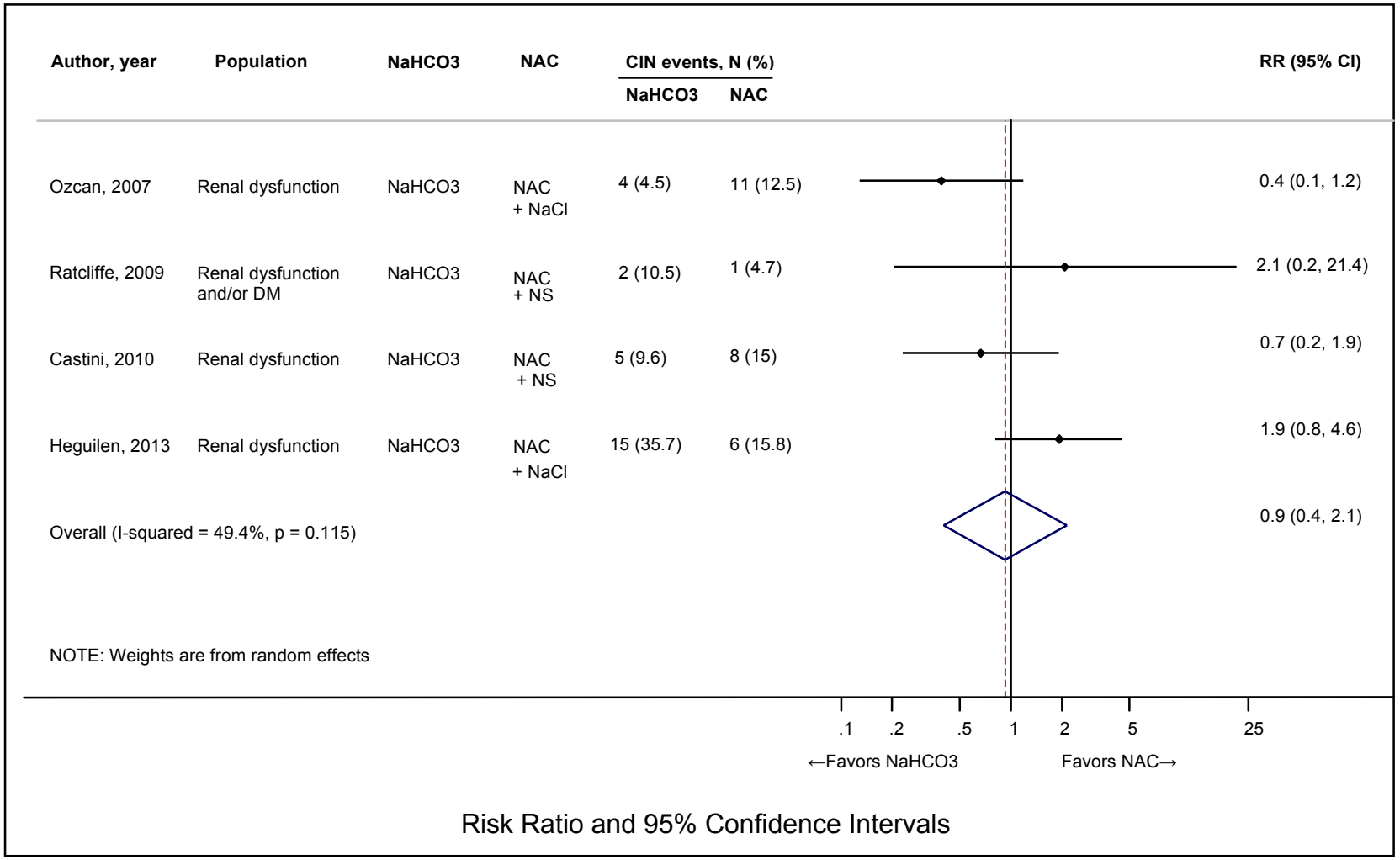


Table 5. Summary of the strength of evidence: N-acetylcysteine versus sodium bicarbonate.

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN, short-term	RCT: 4 (631)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from IV sodium bicarbonate in preventing CIN
Need for RRT	RCT: 2 (420)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from IV sodium bicarbonate in preventing the need for RRT
Cardiac events	RCT: 2 (391)	High	Indirect	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from IV sodium bicarbonate in preventing cardiac events

CIN=contrast-induced nephropathy; IV=intravenous; N=sample size; RCT=randomized controlled trial; RRT=renal replacement therapy

Statins plus Intravenous Fluids versus Intravenous Fluids With or Without Placebo

In addition to decreasing low density lipoprotein cholesterol, statins have cholesterol-independent functionalities that play a growing role in various clinical contexts, including the prevention of both myocardial damage during percutaneous coronary intervention (PCI)[86] and atrial fibrillation after cardiac surgery.[87] The proposed mechanism related to the prevention of CIN is that statins act as stabilizers of the endothelium and as free radical scavengers in ischemic nephropathy.[88] Given the demonstrated pleiotropic nature of statins in clinical settings, it is important to evaluate the effect on CIN and the effects on other outcomes.

Study Characteristics

We found eight studies evaluating the use of statins to prevent CIN.[89-95, 96] All were RCTs and included patients undergoing cardiovascular interventions including PCI,[89, 90, 93 , 94, 95] coronary angiography,[91, 92, 93 , 94, 96] and left ventriculography.[94]

Five studies included patients with reduced kidney function,[91, 92, 93 , 94, 96] three included patients with an acute coronary syndrome,[89, 90, 95] and one included patients with diabetes mellitus.[94] All of the studies were published from 2008[96] to 2013[94] with most followup ranging from 48 hours to 120 hours (5 days) for CIN outcomes and up to one year for other outcomes (Appendix E, Evidence Table 1-3, 19).

All of the studies administered the contrast media intra-arterial. The LOCM agents were iopromide, [89] iobitridol,[90] and iopamidol.[93] Five studies used the IOCM agent iodixanol (Appendix E, Evidence Table 1-3, 19).[91, 92, 94, 95 , 96]

Five studies used atorvastatin,[89-93] two used simvastatin,[95 , 96] and one used rosuvastatin.[94] The statin dose ranged across studies: 80 mg within 24 hours of the procedure[91]; 150 mg administered as 20 mg doses over five days (two days prior to and three days post procedure[94]; two studies administered 80 mg prior to the procedure and 40 mg after the procedure [89, 90]; 40 mg for two days prior to and after the procedure [96]; 80 mg for two days prior to and after the procedure [93]; 80 mg for four days prior to and two days after the procedure [92]; and one study compared 80 mg of a statin to 20 mg of a statin, both doses administered 24 hours prior to the procedure and 48 hours after. [95] Six of the studies compared statins to placebo. [89, 90, 92, 94-96] One study[91] administered N-acetylcysteine to all patients as prophylaxis. One was a head-to-head dose comparison.[95] All statin interventions were given in combination with intravenous fluids such as sodium bicarbonate,[91] normal saline, [89, 90, 92, 94, 95] and half normal saline,[96](Appendix E, Evidence Table 1-3, 19).

Five studies reported on the incidence of CIN at or within 48 hours,[90, 91, 93, 95 , 96] two reported at 72 hours,[89, 94] and one reported at 5 days.[92] Three studies reported on mortality,[91, 92, 94] four on the need for hemodialysis,[91, 92, 94, 96] one on worsening heart failure,[94] and two on the length of hospitalization.[90, 96] Only one study included data on adverse drug effects, specifically elevated liver enzymes (Appendix E, Evidence Table 1-3, 19).[89]

Regarding the quality of the eight studies we examined in this section, one had a high risk of bias,[94] one had low risk, [90] and the remaining six had medium risk.[89, 91-93, 95, 96] The study that had high overall risk of bias raised concerns about the reporting of allocation concealment and selective outcome reporting.[94]

Contrast-induced Nephropathy

Four of the eight identified studies on use of statins to prevent CIN were included in the meta-analysis. Three of the studies excluded from the meta-analysis included N-acetylcysteine in the intervention and control arm or N-acetylcysteine plus sodium bicarbonate in the intervention and control arm.[91-93] One of the studies excluded from the meta-analysis compared different dosages of simvastatin (Appendix E, Evidence Table 20).[95] When evaluating the efficacy of prophylactic statin administration compared with intravenous fluids alone in the prevention of CIN, three studies[89, 90, 94] found both a statistically significant and clinically important reduction in CIN (above our 25% threshold for a minimally important difference) in the intervention arm. One study did not show either a clinically or statistically significant reduction. [96] The largest study of the group with positive findings (n=2998) found a significant reduction with statin administration in the general study population but not in the post-hoc subgroup analyses of statin naïve versus statin non-naïve participants.[94] This study had a high risk of bias but its effect estimate was in the same direction as the other three studies in the meta-analysis and it had a small confidence interval. Another study[92] evaluated the occurrence of CIN within the nonstandard time frame of 5 days; that study did not demonstrate a clinically or statistically significant difference between intervention and control arms (Figure 9).

In a meta-analysis of studies with a CIN endpoint ranging from 48 to 72 hours after contrast media administration,[89, 90, 94, 96] the pooled estimate of the effect of statin plus intravenous fluids compared with intravenous fluids alone demonstrated a clinically important and statistically significant reduced risk of CIN with statin use (pooled RR 0.5, 95% CI: 0.4 to 0.8) with a number needed to treat of 45 (95% CI: 30 to 217). However, the CI for the RR was wide enough that we cannot rule out the possibility of an unimportant difference clinically. A sensitivity analysis demonstrated that no study unduly influenced the overall statistical significance of the pooled estimate, and a stratified analysis showed no substantial difference in estimation of effect by statin type, as the point estimates of effect were all less than 1.0. Only atorvastatin had a 95 percent CI that was fully in the range consistent with a clinically important effect (OR 0.3, 95% CI: 0.2 to 0.7). The estimate for rosuvastatin (RR 0.6, 95% CI: 0.4 to 0.9) was clinically important, but the CI was wide enough to not rule out the possibility of an unimportant effect. While the point estimate of the effect of simvastatin (RR 0.8, 95% CI: 0.2 to 3.4) was not clinically important, the CI was so wide that we could not rule out the possibility of a clinically important benefit or harm. Note that atorvastatin was the only drug for which there was more than one study. Our review showed no substantial difference in stratified analyses by study inclusion criteria for baseline kidney function. Harbord's Modified Test for Small Study Effects did not demonstrate evidence of asymmetry in results by study precision (bias coefficient of -0.82, standard error of 1.14, p =0.55) (Figure 9).

Two studies on statin use incorporated N-acetylcysteine into the treatment regimen of both arms. Neither the study that used N-acetylcysteine plus intravenous sodium bicarbonate as the comparison group[91] nor the studies that used N-acetylcysteine plus intravenous saline as the comparison group[92, 93] found statistically significant reductions in CIN with the use of atorvastatin.

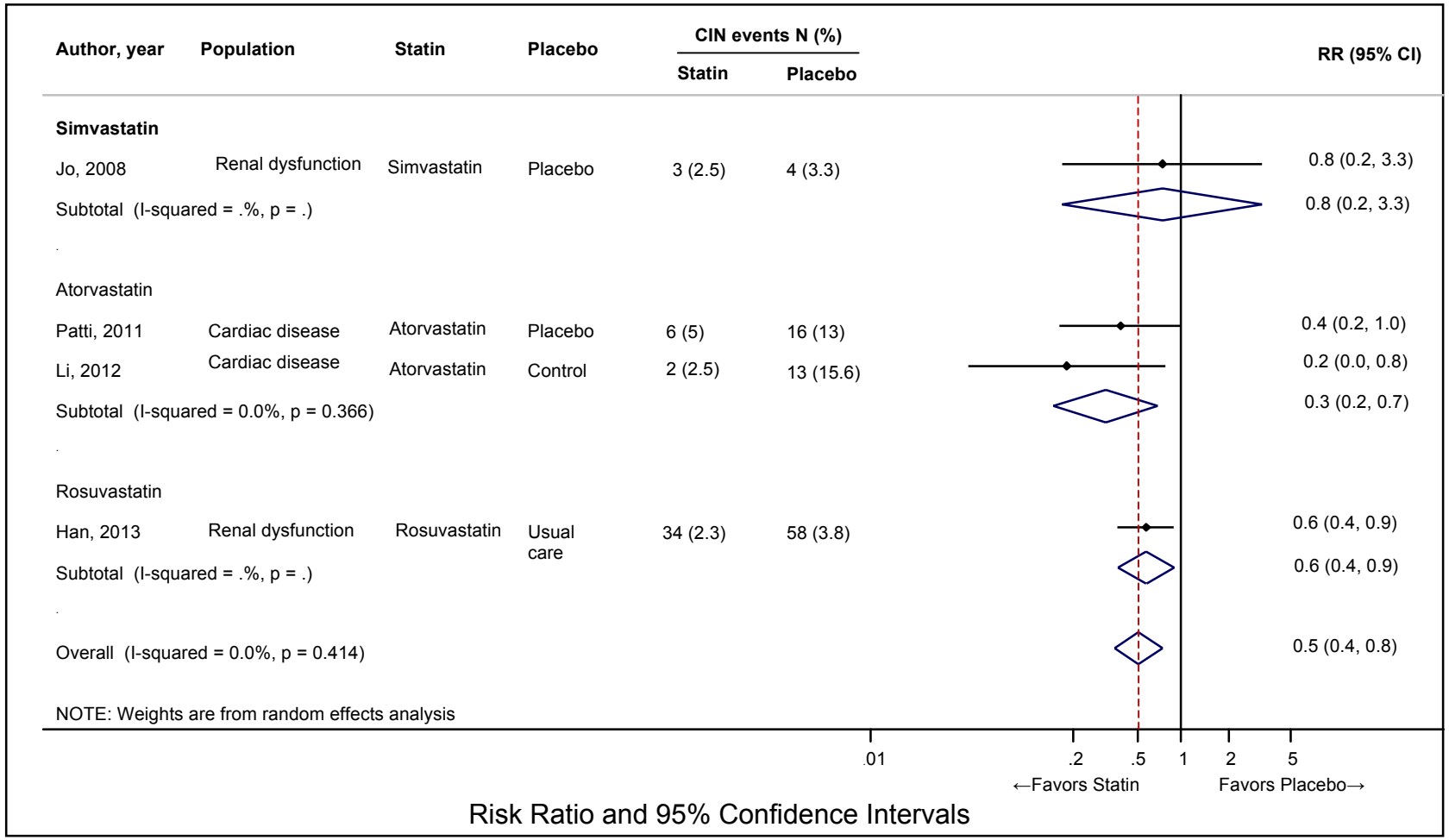
The strength of the evidence for the meta-analysis was moderate for demonstrating that administering a statin plus intravenous fluids was more effective than intravenous fluids alone at preventing CIN, when considering study limitations, directness, consistency, and precision (Table 6).

Other Outcomes

Secondary outcome reporting was not consistent across studies. The strength of the evidence was low about whether statins had an impact on the need for RRT or mortality (Table 6; Appendix E, Evidence Table 21). No clinically important or statistically significant differences were seen in the need for dialysis; very few events were reported.[92, 94, 96] Of the two studies that reported mortality by intervention group, neither showed a statistically significant or clinically important difference; very few deaths were reported.[92, 94] The strength of the evidence was insufficient to determine if statins were effective at reducing length of hospitalization (Table 6; Appendix E, Evidence Table 21).[90]

Adverse events were only reported in one study. We were not able to draw any conclusions about whether the incidence of adverse events differed between statins versus intravenous fluids (Appendix E, Evidence Table 22).[95]

Figure 9. Meta-analysis of statins plus intravenous fluids versus intravenous fluids with or without placebo for the prevention of contrast-induced nephropathy.



%=percent; CI=confidence interval; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; IOCM=iso-osmolar contrast media; IOCM=iso-osmolar contrast media; N=sample size; P=p-value; RR=risk ratio

Table 6. Summary of the strength of evidence: statins plus intravenous fluids versus placebo with or without fluids.

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN, * (meta-analysis)	RCT: 4 (3647)	Medium	Direct	Consistent	Precise	Moderate	Moderate strength of evidence that statins plus IV fluids have a lower risk of CIN than IV fluids alone
Need for RRT	RCT: 3 (5257)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that need for RRT does not differ between statins plus IV fluids compared with IV fluids alone
Mortality	RCT: 3 (3712)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that mortality rates do not differ between statins plus IV fluids compared with IV fluids alone
Hospitalization, length of stay	RCT: 2 (488)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to determine if statins plus IV fluids are more effective at reducing length of hospitalization than IV fluids alone

CIN=contrast-induced nephropathy; IV =intravenous; N=sample size; NA=not applicable; RCT=randomized controlled trial; RRT=renal replacement therapy

* Includes studies examined in meta-analysis because of comparability of intervention and control arms

Adenosine Antagonists plus Intravenous Saline versus Intravenous Saline

Elevated adenosine levels contribute to the pathophysiology of acute reductions in kidney function through induction of renal vasoconstriction after radiocontrast media exposure.[97] Adenosine antagonists belonging to the xanthine drug class, such as theophylline and aminophylline, could theoretically prevent CIN by intervening along this pathway. This would consequently preserve renal blood flow and glomerular filtration perfusion pressure.[98]

Study characteristics

We found a total of five studies, four studies examining the role of the adenosine antagonists theophylline[23, 60, 99, 100] and one study examining the role of aminophylline[53] in the prevention of CIN. All studies were RCTs. Two studies used elevated serum creatinine as an inclusion criterion,[23, 99, 100] one included only those who have at least one risk factor for CIN,[100] one used coronary artery disease as an inclusion criterion,[53] and the remaining study included a population without kidney disease or diabetes mellitus.[60]

All of the studies had a followup between 48[23, 53, 99] and 72 hours[60, 100] for CIN outcomes (Appendix E, Evidence Tables 1-3, 23).[23] The studies were published from 2008[60] through 2012.[100]

When reviewing the characteristics of administered contrast media, one study[60] used intravenous contrast media and the others used intra-arterial administration.[23, 53, 99, 100] Four studies used LOCM agents [53, 60, 100 23] and one study used IOCM[99] (Appendix E, Evidence Tables 1-3, 23).

All studies used theophylline as the adenosine antagonist, except for one which used aminophylline.[53] However, no studies compared theophylline with aminophylline. Three studies[23, 99, 100] used intravenous formulations of theophylline, and one[60] used oral formulations. Two of the six studies had short infusions of theophylline prior to the procedure, ranging from 30 minutes[100] to one hour.[99] Two studies[53, 99] used theophylline intolerance as an exclusion criterion while one[99] excluded patients with prior use of theophylline, and two [23, 100] reported exclusions based on contraindications for theophylline such as history of seizures and high-grade cardiac arrhythmia. All studies used intravenous saline prior to and after the procedure for all comparisons. Intervention drugs were also administered prior to and after the procedure (Appendix E, Evidence Tables 1-3, 23).

Two studies had high risk of bias[23, 60]; two had moderate risk of bias [53, 99]; and one had low risk of bias [100]. Some studies had low scores regarding allocation generation[23, 60], allocation concealment [23, 53, 60], masking of intervention [23, 53, 60], and incomplete outcome reporting[60, 99]

Contrast-induced Nephropathy

Regarding intra-arterial administration of contrast media, the results of our primary analysis were mixed on the incidence of CIN with adenosine antagonists plus intravenous saline versus intravenous saline. Of the three studies that only examined theophylline against intravenous saline, two showed a clinically important increase in CIN in the theophylline group that was not statistically significant,[60, 99] and one demonstrated a clinically important reduction in CIN in the theophylline group that was statistically significant.[100] Other studies looking at intra-arterial administration of contrast media contained multiple comparison arms.[23, 53] In both of the studies

with multiple comparisons, the arms involving the adenosine antagonists had less CIN than the intravenous saline arms; however, one study[23] examined theophylline in combination with N-acetylcysteine and not theophylline on its own (Figure 10).

The meta-analysis exploring all studies involving a comparison between adenosine antagonists and intravenous saline was inconclusive because the CI was so wide that we cannot rule out a clinically important decrease or increase (pooled RR 0.8, 95% CI: 0.1 to 8.2) (Figure 10). The strength of evidence was insufficient to support a conclusion about the effect of adenosine agonists on the risk of CIN because their effects were imprecise and inconsistent, and the study limitations were medium (Table 7).

Only one study examined the effect of theophylline in a population[60] for which contrast media was administered intravenous. It demonstrated a clinically important increased risk of CIN with theophylline that was not statistically significant (Figure 10).

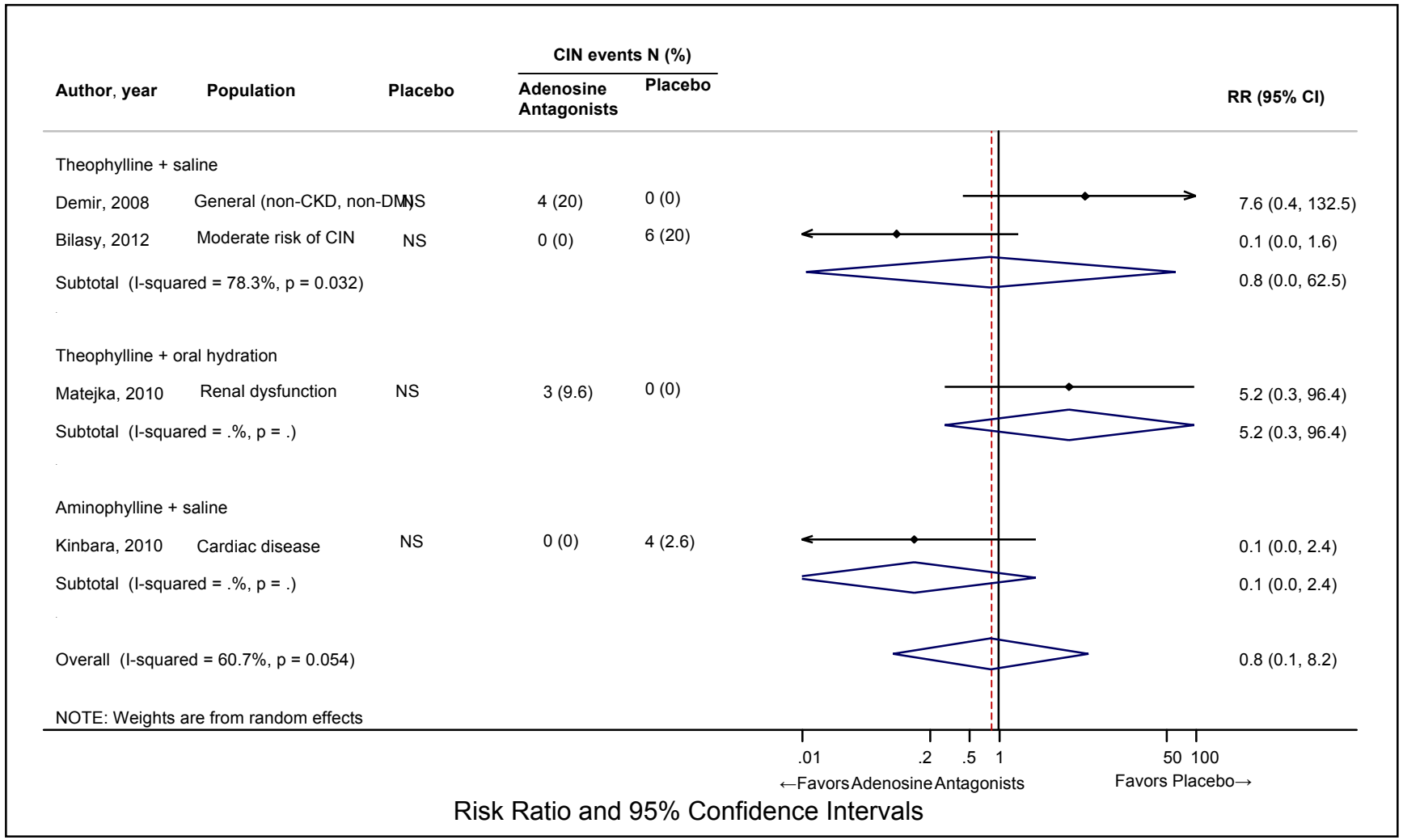
One of the included studies was not included in the meta-analysis.[23] It included N-acetylcysteine in one of the interventions and the p-value was calculated across the three arms (Appendix E, Evidence Table 24).

Other Outcomes

The strength of the evidence was insufficient to determine the effect of adenosine antagonists on the need for RRT, cardiac events, or mortality. No studies reported on length of stay. (Appendix E, Evidence Table 25).

All studies reported on adverse events. Adverse events were not reported in a standardized manner and rarely were they analyzed in these studies, so we were not able to draw any conclusions about whether the incidence of adverse events differed between adenosine antagonists versus fluids (Appendix E, Evidence Table 26).

Figure 10. Meta-analysis of adenosine antagonists plus intravenous saline versus intravenous saline for the prevention of contrast-induced nephropathy.



CI=confidence interval; CIN=contrast induced nephropathy; Mg/dl=milligram per deciliter; N=sample size; P=p-value; RR=risk ratio; SCr=serum creatinine

Table 7. Summary of the strength of evidence: adenosine antagonists plus intravenous saline versus intravenous saline.

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN,* (meta-analysis)	RCT: 5 (3647)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the risk of CIN
Need for RRT	RCT: 3 (314)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the need for RRT
Cardiac events	RCT: 2 (116)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the risk of cardiac events
Mortality	RCT: 2 (273)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the risk of mortality

CIN=contrast induced nephropathy; N=sample size; NA=not applicable; RCT=randomized controlled trial; RRT=renal replacement therapy

* Includes studies examined in meta-analysis because of comparability of intervention and control arms

Renal Replacement Therapy versus Intravenous Fluids

Because contrast media clearance is usually delayed in an impaired kidney, hemodialysis and hemofiltration have been examined as methods to remove more intravenous contrast media for those with CKD in order to reduce the risk of further kidney injury.[101, 102] Studies demonstrate that 2 to 3 hours of hemodialysis effectively removes 60 to 90 percent of contrast media, but the clinical effects were not clear. Continuous venovenous hemofiltration is based on high-volume controlled hydration, which in theory reduces kidney exposure to the contrast media; however patients need to be in an intensive care unit setting for continuous monitoring.

Study Characteristics

We found four studies assessing the use of hemodialysis to prevent CIN[28, 103-105] and two assessing the use of hemofiltration to prevent CIN.[106, 107] All were RCTs and included patients with CKD undergoing cardiovascular interventions. Only one study included patients undergoing additional procedures.[104] All studies used intra-arterial LOCM; 2 studies also administered it intravenous in some of the procedures.[103, 104] The studies were published between 1998 and 2007, with follow up ranging from two weeks to one year.

All hemodialysis studies compared hemodialysis with intravenous fluids, with the hemodialysis arm receiving the same fluid protocol. Normal saline was used in five of the studies, and one study used intravenous glucose plus saline, and added an N-acetylcysteine arm to the comparison.[28]

Hemodialysis was uniformly started after the contrast media was administered, while hemofiltration was started before contrast media administration. In one of these studies, designed to evaluate the timing of hemofiltration, the therapy was done both before and after administration of contrast media (Appendix E, Evidence Tables 1-3, 27).[107]

All studies included patients with various degrees of CKD. Three included patients in advanced stages of CKD (Stages 4 and 5),[104, 105, 107] one included less severe stages of CKD, (Stages 3 and 4)[106] and one study included patients with milder CKD (Stage 3).[28] One study did not provide the CKD stage of the patients, but the inclusion criterion was a mild elevation of serum creatinine (at least 1.4 mg/dl) (Appendix E, Evidence Tables 1-3, 27).[103]

In these studies, the definition of CIN was typically defined as an increase of 0.5 mg/dl above baseline, but the timing for measuring change varied from 24 hours to 6 days. One study did not provide a definition of CIN (Appendix E, Evidence Tables 1-3, 27).[105]

All studies had high risk of bias except for one which had moderate risk of bias.[107] All studies had an increased risk of bias because of the lack of blinding regarding the allocated intervention. Some studies were limited by problems with allocation generation[28, 103-105], allocation concealment, [28, 103-105, 106] and incomplete outcome reporting [103, 104, 106].

Contrast Induced Nephropathy

None of the studies on hemodialysis reported a statistically significant difference between intravenous fluids and hemodialysis in preventing CIN.[103-105] The incidence of CIN was similar in both groups for all of the studies comparing hemodialysis and intravenous saline. The only study assessing hemodialysis plus intravenous glucose and saline[28] found that patients on hemodialysis had higher rates of CIN than those on intravenous saline only and those receiving N-acetylcysteine (15.9% vs 6.1% and 5.3%; $p = 0.008$) at 72 hours, but this effect disappeared

when reassessed thirty to sixty days later. The study found no significant difference in the need for immediate RRT, and none of the patients required long-term RRT. In addition, the study did not find any higher risk of other complications or mortality. Because this study measured creatinine at time points that were different from the other studies, the studies were not comparable (Appendix E, Evidence Table 27).[28] The pooled analysis for the three studies comparing hemodialysis to intravenous saline yielded an aggregate RR of 1.40, consistent with a clinically important increased risk or no important difference (95% CI: 0.9 to 2.2) (Figure 11).

The studies indicated that prophylactic hemodialysis does not prevent the incidence of CIN in patients with CKD, regardless of the stage of CKD, the duration of the dialysis (from 2 to 4 hours), or the time between contrast media administration and initiation of dialysis. No benefit was found when hemodialysis was started before the contrast media was given.[105] The two studies that included results on contrast media clearance[103, 105] demonstrated that peak levels of contrast media were lower in the hemodialysis group than in the control group during the initial hours after contrast media administration, but the effect of dialysis was no longer significant after 72 hours; after 72 hours, elimination half-life was comparable in both arms. This finding correlated with the lack of clinical effect (Appendix E, Evidence Table 28). The strength of evidence was low that hemodialysis does not reduce the risk of CIN and may even be harmful, because the effects of hemodialysis were consistent and direct but imprecise, the magnitude of effect was weak, and the study limitations were high (Table 8).

The study by Frank, et al.[105] was not included in the pooled analysis because it did not provide data for the incidence of CIN. It only reported a non-significant difference between arms (Appendix E, Evidence Table 28).

The studies comparing hemofiltration to intravenous fluids reported that patients with severe CKD may have a lower incidence of CIN. In these studies, this benefit was evident only when hemofiltration was started before the contrast media was administered. As Marenzi, et al.[107] showed, when hemofiltration was started after the contrast media administration, its benefit was lost and the risk for developing CIN was comparable to those patients receiving intravenous saline only. While one study of hemofiltration included more than 50 patients with Stages 3 to 4 CKD per arm and the other study included about 30 patients per arm with severe CKD, the conclusions were similar (Appendix E, Evidence Table 28).

The Harbord's Modified Test for Small Study Effects did not show evidence of asymmetrical effects by study size (bias coefficient of 1.68, standard error of 5.56, p=0.81). The evidence was insufficient to determine whether hemofiltration reduced the risk of CIN in patients with pre-existing severe CKD because of high study limitations, small study size, and the concern that both studies were from the same authors (i.e., not independently replicated). The hemofiltration studies were not combined with the hemodialysis studies in the pooled analysis due to their different designs.

Other Outcomes

The number of complications was low and extremely similar in both intervention arms for hemodialysis studies. Although patients undergoing hemodialysis had a slightly lower risk of pulmonary edema, this risk was not statistically significant (Appendix E, Evidence Table 29); p=0.36[104] and p=NS[105]). They also showed a slight higher but not significant need for emergency hemodialysis, p=0.12 [104], p=0.762[28]. There was no difference between groups in long-term need for hemodialysis and mortality[104]; [28] (Appendix E, Evidence Table 29

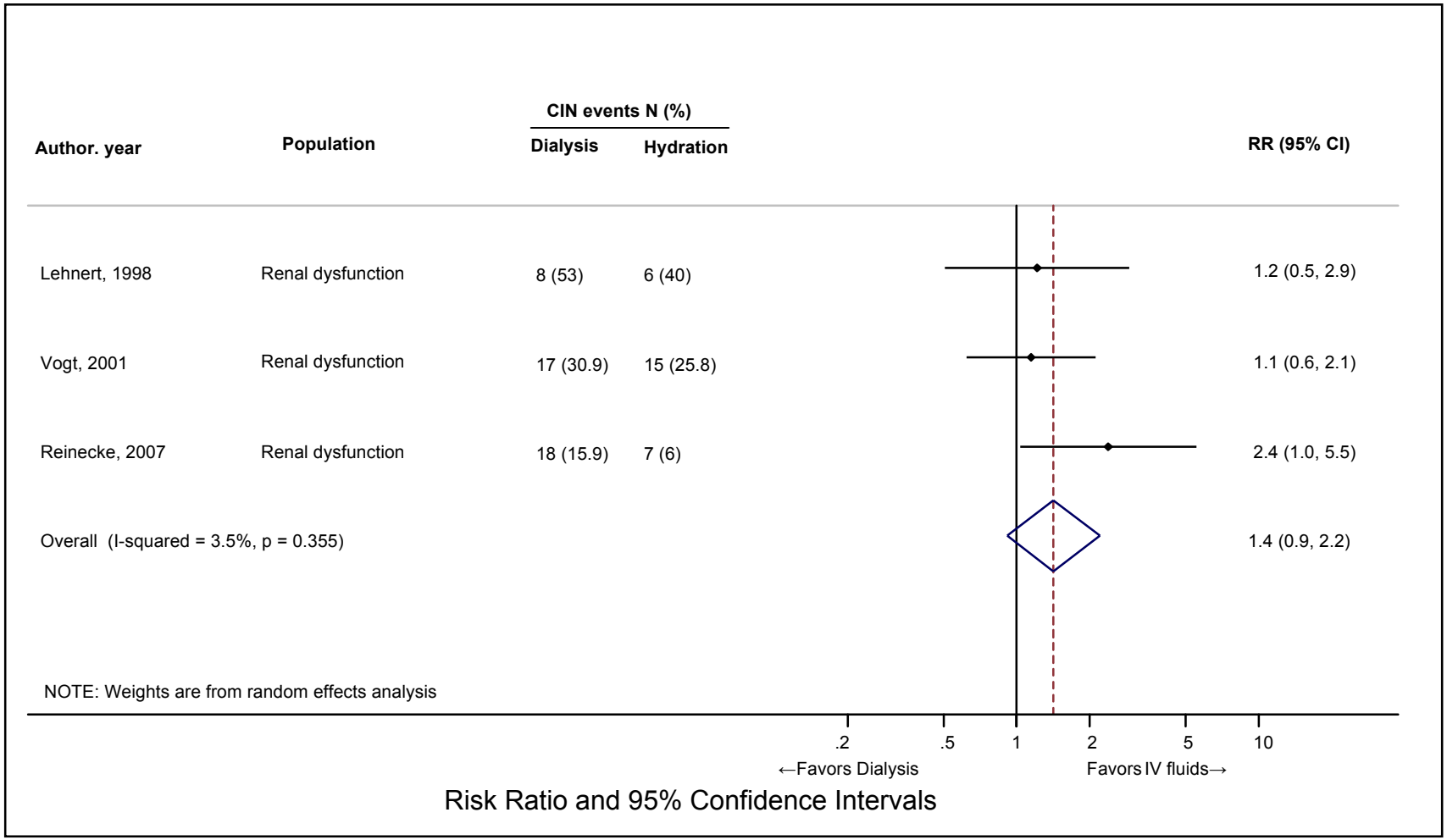
The strength of evidence was insufficient to determine whether hemodialysis reduces the risk of other outcomes due to the heterogeneity of the studies, comparators, and outcomes measured (Table 8).

The studies comparing hemofiltration to intravenous saline demonstrated that patients may benefit from hemofiltration because they have a lower risk of emergency RRT (18% vs 0%, p <0.001)[106] or further RRT, (25% vs 3%, p< 0.001[106] and 30% vs 10%, p=0.02[107]), and lower risk for mortality(14% vs 2%, p=0.02)[106] . This benefit was evident only when hemofiltration was started before contrast media was administered. As Marenzi et al.[107] showed, when hemofiltration was started after the administration of contrast, its benefit is lost and the risk for developing CIN is comparable to those patients receiving hydration only. Another confounder for these studies may be the use of bicarbonate instead of saline (Appendix E, Evidence Table 29). There was, however, a limitation to this group of studies; the studies that compared hemofiltration versus intravenous fluids were confounded by the use of intravenous bicarbonate with the hemofiltration. Insufficient evidence is available to support the conclusion that hemofiltration reduces the need for RRT (Table 8).

The strength of evidence was insufficient that RRT (either hemofiltration of hemodialysis) reduces the risk of other outcomes due to the heterogeneity of the studies, comparators, and outcomes measured (Table 8).

Adverse events were reported in five studies (Appendix E, Evidence Table 30). [28, 56, 104, 105, 108] The main adverse events reported were hematomas, blood loss, and urinary retention and/or anuria. Adverse events were not reported in a standardized manner and rarely were they analyzed in these studies, so we were not able to draw any conclusions about whether the incidence of adverse events differed between patients receiving RRT and those who did not.

Figure 11. Meta-analysis of hemodialysis versus intravenous fluids for the prevention of contrast-induced nephropathy.



%=percent; CI=confidence interval; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; Cr=creatinine; IV=intravenous; LOCM=low-osmolar contrast media;

Table 8. Summary of the strength of evidence: RRT versus fluids.

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN HD studies,	RCT: 4 (584)	High	Direct	Consistent	Imprecise	Low*	Low strength of evidence that hemodialysis does not decrease the risk of CIN compared to IV fluids
Development of CIN HF studies,	RCT: 2 (206)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Development of CIN, (all studies)	RCT: 6 (790)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Need for RRT HD studies	RCT: 3 (752)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Need for RRT HF studies	RCT: 2 (206)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Cardiac events HD studies	RCT: 2 (130)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Cardiac events HF studies	RCT: 1 (114)	Medium	Direct	Insufficient	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Mortality HD studies	RCT: 2 (537)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Mortality HF studies	RCT: 2 (206)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion

CIN=contrast-induced nephropathy; HD=hemodialysis; HF=hemofiltration; RCT=randomized controlled trial; RRT=renal replacement therapy

*The strength of evidence was graded as low rather than insufficient because the results were precise enough to rule out a clinically important benefit. The results were not precise enough to determine whether hemodialysis produced an increase or no difference in the risk of CIN

Miscellaneous Comparisons

Many studies identified in our search did not fall into any of the main comparison groups listed above. We identified these comparisons as miscellaneous and categorized them into the following groups: N-acetylcysteine versus other interventions; sodium bicarbonate versus other interventions; N-acetylcysteine plus sodium bicarbonate versus other interventions; diuretics versus other interventions; vasoactive drugs versus other interventions; antioxidants versus fluids; dopamine versus other interventions; and head-to-head comparisons of different regimens for giving fluids. We summarized the findings of these miscellaneous comparisons below. All studies investigated the impact of the interventions on CIN. Full details are in Appendix H, Miscellaneous Comparisons; Appendix I, Evidence Tables for Miscellaneous Comparisons.

N-acetylcysteine versus Other Interventions

We found 23 studies comparing N-acetylcysteine with other interventions including ascorbic acid,[19, 109] nebivolol,[110] atorvastatin,[93] aminophylline,[53] theophylline,[23, 60, 111] fenoldopam,[38, 112, 113] misoprostol,[60] intravenous fluids,[28, 42, 84, 114] and dialysis. [24] There was substantial heterogeneity across these studies in terms of: dose of N-acetylcysteine; dose, type and duration of intravenous fluids; sample size; and followup period. The definition of CIN varied across studies as well. Because of the large heterogeneity of studies, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H, and I.

Sodium Bicarbonate versus Other Interventions

We found five studies comparing sodium bicarbonate with other interventions not involving N-acetylcysteine.[115-119] The comparison interventions included acetazolamide,[118] long-term versus short-term sodium bicarbonate,[115] sodium bicarbonate in five percent dextrose versus normal saline in 5 percent dextrose,[119] intravenous sodium bicarbonate versus oral sodium bicarbonate,[116] and saline versus saline plus sodium bicarbonate. Two studies used IOCM, two used LOCM, and one used both LOCM and IOCM. There was considerable heterogeneity across studies in terms of dose of sodium bicarbonate, dose and duration of other comparators, sample size, and follow-up period. All studies with the exception of one defined CIN as an increase of serum creatinine of 25% or at least 0.5 mg from baseline. Because of the large heterogeneity of studies, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H, and I.

N-acetylcysteine plus Sodium Bicarbonate versus Other Interventions

We found seven studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions.[42, 84, 109, 120-123] In all studies, sodium bicarbonate was given intravenous at 3 ml/kg/hour or at 1 ml/kg/hour, before and after contrast media administration. A total of two doses of N-acetylcysteine was given prior to and after contrast media administration. All studies used nonionic IOCM. However, two studies also included administration of LOCM. N-acetylcysteine plus sodium bicarbonate was compared to N-acetylcysteine plus normal saline,[109, 122] Renal Guard,[120] sodium bicarbonate plus dextrose,[84] or sodium bicarbonate alone.[121] The

study population for all trials was comprised of patients with renal dysfunction who were undergoing coronary interventions or another major arteriographic procedure, and three of the studies only included patients with Stage 3or Stage 4 CKD.[84, 120, 121] Due to the substantial heterogeneity of the comparators, and follow-up periods, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H, and I.

Diuretics versus Other Interventions

We found three studies comparing the use of different diuretics (furosemide, mannitol, and acetazolamide) in combination with intravenous saline to prevent CIN.[11, 118, 124] All studies included patients undergoing cardiovascular interventions and all studies included patients with diabetes mellitus. Two studies used LOCM and one used IOCM. Two studies evaluated furosemide as the diuretic of interest.[11 , 124] These two studies used it as a single comparator[11, 124] Diuretic administration was given intravenous in all of the studies, but the protocols and doses varied. One study evaluated the effects of mannitol,[11] and another included acetazolamide. Due to the substantial heterogeneity of the comparators, and follow-up periods, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H, and I.

Vasoactive Agents versus Other Interventions

We found eight studies comparing vasoactive agents to other interventions: four studies on fenoldopam [38, 112, 113, 125]; two on calcium antagonists (one with nifedipine),[60] one with the combination of amlodipine and valsartan, an angiotensin receptor blocker)[126]; one on benazepril (an ACE inhibitor),[127] and one on nevibolol (a beta blocker).[110] One study included only patients undergoing CT imaging,[60] the remainder of the studies included patients undergoing cardiovascular interventions. All studies included patients with diabetes mellitus, but only one performed subgroup analysis for this population.[113] Four studies use LOCM, three used IOCM, and one used both IOCM and LOCM. The studies were very heterogeneous, from the medications included to the doses used. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H and I.

Antioxidants versus Hydration

We found five studies evaluating different antioxidant strategies for preventing CIN. The antioxidant probucol was evaluated in two of these studies,[128, 129] while the other three investigated pentoxifylline, an antioxidant and anti-inflammatory agent,[130] sodium-2 mercaptoethanesulfonate (MESNA), a scavenger of reactive oxygen species,[131] and zinc, which has the potential to act as an "endogenous antioxidant" via increasing metallothionein[46]. All were conducted in patients with impaired renal function (serum creatinine greater than 1.2 and less than 3.0 mg/dl) undergoing coronary interventions and receiving LOCM. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H and I.

Fluid Interventions

We found 11 studies comparing different fluid regimens.[116, 132-141] Notably, two studies compared fluids to no fluids, with one comparing 0.45% saline[137] and the other investigating normal saline.[133] Three compared oral fluids to intravenous normal saline,[116, 132, 140] and two compared isotonic saline to hypotonic saline.[135, 141] The timing of hydration, whether prior to or after the procedure, was compared in two studies.[133, 138] Saline was separately compared with dextrose or sodium bicarbonate in three studies. (Appendix I; Evidence Tables A-C; P1).[133, 136, 139] All of these studies defined CIN as an increase in serum creatinine by 25 percent or a change in serum creatinine of 0.5mg from baseline at 48 or 72 hours. However, one study also used an increase of glomerular filtration rate from a baseline of 50 percent.[138] A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H, and I.

Dopamine versus Other Interventions

We found three studies assessing the effectiveness of dopamine in reducing CIN in patients with impaired renal function.[142-144] One of the studies compared dopamine and a placebo,[144] and another compared a combination of dopamine and furosemide to a combination of dopamine, furosemide, mannitol, and saline.[143] The remaining study had three arms that compared dopamine, saline, and aminophylline.[142] In all of the studies, dopamine was administered prior to and after contrast media administration. In two of the studies, the dose of dopamine was 2.5 microgram/kg/min,[142, 144] and the other study uses a dose of 3 microgram/kg/ml.[143] One study had no definition set for CIN,[143] while the other studies defined CIN as a change in serum creatinine greater than or equal to 25 percent or greater than 0.5 mg from baseline. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H and I.

Discussion

We performed a comprehensive review of all major interventions to prevent contrast-induced nephropathy (CIN) that are explored in the literature. In this section, we highlight the interventions for which evidence of a clinically important benefit is strongest and provide commentary on the limitations of the evidence as well as the manner in which our review results compare with the findings of previous reviews that examined selected portions of this large body of evidence. We also discuss the implications of our findings for clinicians, investigators, and policy makers (e.g., professional societies that set guidelines on the use of contrast media, and health plans that make decisions about coverage for interventions).

N-acetylcysteine plus Intravenous Saline versus Intravenous Saline With or Without Placebo

N-acetylcysteine is a thiol compound with both antioxidant and vasodilatory properties. Our meta-analyses indicated that N-acetylcysteine provides a small clinically important benefit in reducing the risk of CIN when a high dose is used, although the strength of the evidence was low. These findings are similar to previously published meta-analyses.[145, 146] Although prior meta-analyses have demonstrated the benefits of N-acetylcysteine, our analysis separated the effects of low dose N-acetylcysteine and high dose N-acetylcysteine. It appears the effect of high dose N-acetylcysteine is slightly greater than the effect of low dose N-acetylcysteine, with the difference being enough to produce a clinically important benefit.

Stratified analyses demonstrated that both low doses ($\leq$ 1200 mg/day) and high doses (> 1200 mg/day) of N-acetylcysteine yielded a small decrease in the incidence of CIN, especially when the contrast media was administered intra-arterial. However, contrary to a recently published meta-analysis,[147] our analyses did not demonstrate a clear benefit of administering N-acetylcysteine for patients receiving intravenous contrast media. This difference may be due to methodological variations among the studies. The recently published meta-analysis[148] included studies in which CIN was defined not only by change in serum creatinine but also by changes in cystatin C. In addition, in some of the studies included in the meta-analysis, the timeframe for the definition of CIN was longer than 72 hours. More studies are needed to investigate whether there is any benefit of administering N-acetylcysteine to patients receiving an imaging test when the contrast media is administered intravenous.

Another critical point is that Wu et al, 2013[149] found that the risk of CIN was reduced with N-acetylcysteine in patients with a baseline serum creatinine greater than 1.2 mg/d. They did not find a benefit of N-acetylcysteine in low-risk patients. Our meta-analysis was not limited to individuals with kidney disease. We did not have patient level data to do stratification analysis based on serum creatinine level. Therefore, a potential benefit in patients without CKD cannot be excluded. Pretest serum creatinine level is an important covariate associated with CIN and this needs further focused studies to systematically elucidate whether a standard dose of N-acetylcysteine would be beneficial in patients with high preexisting serum creatinine level.

Our stratification analysis showed a particular benefit of N-acetylcysteine in reducing the incidence of CIN when LOCM is used for intra-arterial contrast studies. There was no evidence

for a clear benefit of administering N-acetylcysteine intravenous versus administering it orally.

Because of the great variability in study protocols as well as the conflicting results of the available clinical trials, the recommendations for N-acetylcysteine administration vary by organization. For example, the joint American College of Cardiology/American Heart Association 2012 guidelines do not recommend the use of N-acetylcysteine for patients receiving intra-arterial contrast in cardiac procedures.[150] However, the 2012 Kidney Disease: Improving Global Outcomes *(*KDIGO*)* Clinical Practice Guideline for Acute Kidney Injury report recommended using oral N-acetylcysteine with intravenous fluids in patients at increased risk for CIN.[150] The KDIGO recommendation is based on the argument that although the overall benefit for N-acetylcysteine is not consistent or overwhelming, it is inexpensive, appears to be safe, and has been shown in many studies to have an effect in reducing the risk of CIN.[151] Although our analysis did not reveal a difference in effectiveness according to the baseline risk of CIN, it does provide low strength of evidence consistent with the KDIGO recommendation that administering N-acetylcysteine at high dose may have a small clinically important benefit.

Sodium Bicarbonate versus Intravenous Saline

It has been hypothesized that sodium bicarbonate may be preferable to other forms of intravenous fluids because alkanization may protect against free radical injury. Our meta-analysis on this topic demonstrated with low strength of evidence that intravenous sodium bicarbonate did not differ from intravenous saline in the incidence of CIN, although the CI for the aggregate effect estimate was not precise enough to rule out the possibility of a clinically important benefit with sodium bicarbonate. Our results are in contrary to the conclusion of a recent meta-analysis including 19 clinical trials [72] investigating the effect of intravenous sodium bicarbonate. Our analysis included 13 RCTs which compared intravenous sodium bicarbonate versus intravenous saline. In comparison, the other meta-analysis also included five studies with combination regimens of intravenous sodium bicarbonate and N-acetylcysteine. This difference in the included studies helps to explain why we did not find a clinically significant effect size favoring intravenous sodium bicarbonate administration.

The strength of evidence also was low that intravenous sodium bicarbonate did not produce a clinically important reduction in mortality or the need for RRT when compared with intravenous saline. The evidence was insufficient to support conclusions about whether intravenous sodium bicarbonate differs from intravenous saline in the effect on cardiac events or length of hospitalization. The optimal timing and amount of fluid administration is also not established.

N-acetylcysteine plus Intravenous Saline versus Intravenous Sodium Bicarbonate

We found four RCTs[21, 38, 51, 84] addressing the effects of N-acetylcysteine with concurrent administration of intravenous saline compared with intravenous sodium bicarbonate. However, the evidence was insufficient to support a conclusion about the comparative effectiveness of these two interventions in their ability to prevent CIN. We found no other meta-analyses on this head-to-head comparison. Limitations of the head-to-head comparison of N-acetylcysteine with concurrent administration of intravenous saline compared with intravenous sodium bicarbonate include small number of studies, the varying regimens of fluid administration and N-

acetylcysteine dosing, the variations in follow-up time and variation in inclusion criteria which predisposes to CIN, as we described in the result section.

However, in another part of our analysis, we found low strength of evidence for a clinically important decrease in CIN with high dose N-acetylcysteine plus intravenous saline compared with intravenous saline alone, and low strength of evidence for no important difference in CIN risk between intravenous sodium bicarbonate intravenous saline. This indirect evidence may favor administration of N-acetylcysteine in the prevention of CIN, though we have insufficient evidence now based on direct head-to-head comparison of N-acetylcysteine and sodium bicarbonate. If additional studies are done to assess the comparative effectiveness of these two interventions, it would be important to focus on comparing intravenous sodium bicarbonate to high dose N-acetylcysteine with intravenous saline. Again, it would be important to investigate this in patients with a high baseline serum creatinine in whom the risk of developing CIN is higher.

Statins plus Intravenous Fluids versus Intravenous Fluids With or Without Placebo

Several observational studies suggest the possibility that statins may reduce the incidence of CIN. It has been proposed that this finding may be due to the potentially favorable effects on endothelial function, oxidative function, arterial stiffness, and inflammation. We found eight RCTs evaluating the use of statins to prevent CIN. Our results showed a statistically significant protective effect against CIN when statins are administered in combination with intravenous fluids compared with intravenous fluids alone. We saw this treatment effect in populations with chronic kidney disease (CKD)[91-94, 96] or diabetes mellitus[94] that are undergoing intra-arterial contrast media administration for coronary angiography and/or coronary interventions. Overall, the strength of evidence was moderate for the finding that statins given with intravenous fluids are more effective than intravenous fluids alone at preventing CIN.

These results are consistent with five[152-156] out of eight recent meta-analyses on the same comparisons.[152-159] Two of the meta-analyses showing significant decreases in CIN in the statin group only saw the decrease in patients with CKD greater than stage 3.[153, 154] All of the studies included in our meta-analysis were included in the previous meta-analyses with the addition of two more recent studies by Quintavalle et al., 2012[91, 111] and Han et al., 2013.[94] One of these was a large study showing significant decreases in the incidence of CIN in the arms receiving statins.[94]

The oldest study included in our meta-analysis was published in 2008.[96] Based on this review, the dose and duration of statin administration for prophylaxis against CIN has not changed over the last 5 years. The most important factor to note in this investigation and in previous investigations is that statins appear to protect patients against CIN. Currently, protocols for prevention of CIN in the United States do not include the use of statins, despite these results and increasing recognition of the beneficial cholesterol-independent vascular effects of statins. It may be time to reassess the role of statins in preventing CIN, especially since statins are readily available, easy to administer, and relatively inexpensive.

Adenosine Antagonists plus Intravenous Saline versus Intravenous Saline

Elevated adenosine levels can lead to renal vasoconstriction after contrast media exposure, so it has been proposed that adenosine antagonists, such as theophylline and aminophylline, could prevent CIN. We found four RCTs examining the role of theophylline and one examining the role of aminophylline in the prevention of CIN. All trials used intravenous normal saline in both treatment groups. Our analyses showed insufficient evidence to demonstrate an overall treatment effect of theophylline or aminophylline plus intravenous saline when compared with intravenous saline alone for the prevention of CIN. There were wide variations in the effect estimates for individual studies, ranging from a ten-fold decrease in the risk of developing CIN with theophylline [100] to an almost 6-fold increase in the risk of developing CIN with theophylline.[99] Although our test of heterogeneity demonstrated that almost half of the uncertainty in the latter estimate could be explained by differences between studies, the p-value around this estimate was not statistically significant. Clinically, the variation could be explained by the heterogeneity of the populations in the studies, which ranged from patients with stable coronary artery disease[53] to those with moderate to severe CKD.[23] A previous meta-analysis showed that the administration of theophylline or aminophylline was associated with less of a decline in kidney function than if it was not given. [160] However, intravenous saline was not administered in all the studies. In addition, the authors were unable to comment on the incidence of CIN based on the information provided in the articles. The authors of a meta-analysis looking at the effects of theophylline reported a trend toward a reduction in the incidence of CIN with theophylline use, but noted that the findings were inconsistent across studies. [161]

Overall, the evidence on the effects of adenosine antagonists on CIN was limited by medium to high risk of bias in the studies, and considerable inconsistency and imprecision in the effect estimates. Only one of the relevant studies looked at intravenous contrast media administration; this may be relevant because the effect of prophylactic agents on CIN may differ depending on the method of contrast media administration. [162, 163] The evidence also suffered from a lack of reporting on secondary outcomes such as need for dialysis, prolonged hospitalization, in-hospital mortality, and adverse drug effects. In this situation, the evidence seems insufficient to support much investment in further studies of the use of adenosine antagonists in preventing CIN.

Renal Replacement Therapy versus Intravenous Fluids

Hemodialysis and hemofiltration are invasive and expensive procedures that carry risks, but can remove some of the administered contrast. However, it is not known if this contrast removal actually leads to a clinical benefit in terms of decreasing the incidence of CIN. Our analyses did not demonstrate a decreased incidence of CIN in individuals receiving hemodialysis. A previous meta-analysis by Cruz et al actually demonstrated a potentially increased risk of CIN in patients receiving hemodialysis.[164] However, limitations of the studies we found include small sample size, lack of rigorous controls, and uncertainties about the magnitude of delays between contrast administration and initiation of hemodialysis.

The studies comparing hemofiltration to intravenous saline reported that patients with severe CKD may have a lower risk for CIN with hemofiltration, especially when hemofiltration is

started before the contrast media administration. These conclusions are limited by the fact that we only found two studies reporting this, and both are from the same authors and same institution. Another limitation is that the control groups received intravenous saline, while the patients undergoing hemofiltration received intravenous sodium bicarbonate as part of the procedure. Hemofiltration is expensive and requires patients to be admitted to and monitored in an intensive care unit. Furthermore, based on the design flaws in the reported trials and the paucity of studies examining this, further research is needed before proposing to expose patients to this invasive procedure as a standard prophylactic measure. It is important to note that the benefit of hemofiltration was only seen in these studies when it was initiated before the contrast media was given. Therefore, any added benefit is not from removal of the contrast media, and it is proposed that the benefit may be secondary to the ability to provide more vigorous hydration. Clinical trials comparing hemofiltration with intravenous fluid protocols, and stronger trials that include investigation of the pharmacodynamics of the contrast media elimination during hemofiltration, may help better understand this procedure and its benefits.

Several additional limitations should be noted. Renal injury after contrast media administration occurs rapidly, and in these studies, hemodialysis may have been started too late to provide a significant benefit. Furthermore, the removal of creatinine by hemodialysis or hemofiltration limits the assessment of CIN as an outcome. However, while a false decrease in serum creatinine due to hemodialysis or hemofiltration is expected to bias the results toward a protective effect on the incidence of CIN, the results for hemodialysis actually suggested possible harm. The lack of a clinical benefit of RRT may also be secondary to possible adverse events directly caused by the procedure (e.g., hypotension that may worsen kidney injury). Based on these results and the limitations and risks of the procedures, evidence is insufficient to support a clinically important benefit of RRT.

Our findings coincide with the previously published systematic review by Cruz,[164] which concludes that RRT does not provide any protection against CIN. That systematic review included additional studies that did not meet our inclusion criteria (a total of nine RCTs and two non-randomized RCTs).

Miscellaneous Comparisons

Many studies identified in our search did not fall into any of the main comparison groups listed above. For all of the miscellaneous comparisons, we were unable to support conclusions on the effectiveness of one intervention versus the other in preventing CIN.

Surprisingly little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving intra-vascular contrast media, despite the fact that current clinical practice often involves use of oral hydration alone. Oral hydration is a simple and potentially cost-effective strategy for preventing CIN, if proven to be as effective as intravenous saline. Unfortunately, few studies investigated oral hydration versus intravenous saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus intravenous saline, especially for intra-arterial contrast procedures such as coronary angiography.

Overall Limitations

One of the biggest limitations of our systematic review is the marked heterogeneity of the study protocols, populations, definitions of CIN, and follow-up times in the studies. The heterogeneity limited our ability to assess all of the comparisons of interest. Because studies varied in their use and definition of kidney insufficiency as an inclusion criterion, and often did not report results stratified by baseline kidney function, it was very difficult to assess how the effectiveness of interventions might vary according to baseline kidney function. The studies generally did not report results in a manner that would permit assessment of how the effects of interventions might differ by other characteristics of patients. Also, some of the studies we found were excluded because their definition of CIN did not match our pre-specified definition; this is one of the reasons why our findings sometimes differed from those of other meta-analyses.

A second major limitation is that it is very difficult to apply the existing evidence to patients receiving intravenous contrast media because the vast majority of studies focused on patients receiving intra-arterial contrast media. It is possible that the risk of CIN is very low with the LOCM and IOCM protocols now used routinely with intravenous imaging. However, studies generally did not report results in a way that allows for determination of how the effects of interventions might differ by differences in the type, route, or volume of contrast media used.

A third limitation is that studies were very inconsistent in reporting on longer-term clinical outcomes that would be more important to patients than whether their serum creatinine level increased or their GFR decreased. In general, the evidence was insufficient to support conclusions about the comparative effects of interventions on long-term clinical outcomes.

Finally, the results of the review are susceptible to bias in the available evidence. Many of the included studies had medium or high risk of bias, including problems with selection bias (from inadequate methods for allocating patients to treatment assignments), detection bias (from limited blinding of outcome assessments), attrition bias (from incomplete outcome assessments), and reporting bias (from selective reporting of outcomes). In addition, publication bias is a concern in this body of literature, as reported by Vaitkus et al., 2007[165] who showed that the estimated effectiveness of N-acetylcysteine was greater in published articles than in unpublished abstracts. Despite our extensive search, we may have missed studies that have not been presented in a publicly available forum. Although we did not find evidence of asymmetry of results by study precision, statistical techniques have limited ability to detect publication bias. In general, we would expect the overall results of existing biases in this body of evidence to lead to an over-estimate of the effectiveness of interventions.

Future Research Section

Future studies of the comparative effectiveness of interventions for preventing CIN should stratify patients according to their baseline risk of CIN, especially since it may be difficult to detect a difference in patients having a low risk of CIN. Patients with normal or near normal serum creatinine may have a lower risk for developing CIN compared to those with higher serum creatinine levels. Also, patients with risk factors for CKD may have a higher risk of developing CIN than patients without such risk factors. Unfortunately, we had a limited ability to stratify the

analysis according to baseline risk because almost all studies had a mixed patient population and did not report the results separately by baseline risk.

Since the evidence for a small benefit from high-dose N-acetylcysteine was not strong, more research is needed in this area. Future research could examine whether the effectiveness of high-dose N-acetylcysteine differs by route of administration (oral versus intravenous), timing of administration (before versus after the procedure), or baseline risk of developing CIN. Given the evidence that intravenous sodium bicarbonate did not differ from intravenous saline in the incidence of CIN, it may be difficult to justify additional RCTs of intravenous sodium bicarbonate unless new evidence emerges to suggest that particular regimens for administering sodium bicarbonate are more effective than the usual administration of intravenous saline, or that sodium bicarbonate has a benefit for particular groups of patients having a higher risk of developing CIN.

The clinically important benefit of statins demonstrated in this analysis provides a rationale for further studies investigating whether the effect differs by statin dose, timing of administration, or baseline risk of the patient population. Further investigation into the findings on statins versus hydration could be performed through examination of the possible effect of modifiers such as baseline kidney function, type of contrast media, statin dosage, concurrent use of nephrotoxic medications, and patient demographics.

Little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving contrast media, despite the fact that current clinical practice often involves use of oral hydration alone for studies performed with intravenous contrast media administration. Oral hydration is a simple and potentially cost-effective strategy for preventing CIN, if shown to be as effective as intravenous saline. Unfortunately, very few studies investigated oral hydration versus intravenous saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus intravenous saline, especially for intra-arterial contrast procedures such as coronary angiography.

It is very difficult to apply the existing evidence to patients undergoing procedures with intravenous contrast media administration because the vast majority of studies focused on patients receiving intra-arterial contrast media. The risk of CIN may be low enough with the intravenous administration of LOCM and IOCM to make it very difficult to demonstrate the effectiveness of an intervention for preventing CIN. To determine the effectiveness of interventions for preventing CIN in patients receiving intravenous contrast media, it may be necessary to perform large studies of patients having risk factors for developing CKD.

More good quality, head-to-head trials are needed to identify the most efficacious regimen for preventing CIN based on an accepted definition of CIN and consideration of subsequent outcomes that are important to patients, especially in patients at increased risk for developing CIN. Additional questions that still need to be addressed include whether or not low-risk individuals (e.g., without diabetes mellitus or other risk factors for developing kidney disease) could benefit from any prophylactic treatment, and whether the minimum standard for administering fluids or other interventions to prevent CIN should be different for intravenous versus intra-arterial administration of contrast media.

Finally, there is paucity of data for other outcomes in the current reported trials. Critical for future studies is more standardized reporting on adverse outcomes such as drug side effects, need for hemodialysis, length of hospitalization, and mortality. This would aid in the compilation of a more complete risk-benefit profile, allowing for assessment of comparable interventions in this clinical setting.

Conclusions

The optimal therapy to prevent CIN is uncertain despite being the topic of numerous studies. The most accepted method for preventing CIN at this time involves use of intravenous fluids, though there is no consensus regarding the ideal type of fluids or the ideal regimen for administering fluids. Of all the other interventions that have been used to reduce the risk of CIN, the only ones with evidence of a clinically important benefit over use of intravenous fluids alone are high-dose N-acetylcysteine with intravenous saline, and statins with intravenous fluids. N-acetylcysteine is recommended by some organizations because it is an inexpensive drug that appears to be safe and may be beneficial in protecting against CIN. The ideal dose and method of administration of N-acetylcysteine is not known. We are not aware of any guidelines recommending use of statins to prevent CIN despite moderate strength of evidence that statins have a beneficial effect.

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